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IN THEIR CONTRIBUTIONS

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JANUARY 1942

BASIC HEMODYNAMIC PRINCIPLES
ESSENTIAL TO INTERPRETATION OF
CARDIOVASCULAR DISORDERS*

The Ludwig Kast Lecture

CARL J. WIGGERS

Professor of Physiology and Director, Dept. of Physiology
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GRAHAM LUSK¹ related that when the founding of the Harvey Society was first proposed, Samuel J. Meltzer expressed grave doubts whether New York physicians could be conditioned to attend scientific lectures. "New York," he said, "is a city devoid of scientific interest. The Academy of Medicine is not a scientific body and has no interest in scientific medicine." The growing popularity of the annual Graduate Fortnight, sponsored by your Academy, certainly attests that this has not been true for some time. Their inauguration was, I understand, due chiefly to the foresight and enthusiasm of Dr. Ludwig Kast, in whose honor and memory these lectures are given. I feel significantly honored by the privilege of delivering such a lecture this evening.

Among the books which I treasure is one purchased at the very beginning of my medical career (1904). It is by Theodore C. Janeway, and its full title reads, "The Clinical Study of Blood Pressure—A Guide

* Delivered October 13, 1941 at the Graduate Fortnight of The New York Academy of Medicine.

to the Sphygmomanometer in Medical, Surgical and Obstetrical Practice, with a Summary of Experimental and Clinical Facts Relating to Blood Pressure in Health and Disease." Janeway reviewed the salient facts of hemodynamics as they were known in that day and upon them built interpretations of blood pressure readings in clinical practice. Only a Janeway could have produced so outstanding a monograph. Its influence in establishing routine blood pressure determinations in the practice of medicine and in our progressive advance in the interpretation of hypo- and hypertension is immeasurable.

During the thirty-seven years that have elapsed, significant contributions of a fundamental nature have been made in our understanding of dynamic aspects of blood pressure and its physiological control. However, a fairly large experience in reading and evaluating publications dealing with the heart and circulation has convinced me that physicians, clinicians, and experimenters, otherwise distinguished, frequently neglect these fundamental principles of hemodynamics in drawing conclusions, while comparatively few utilize the possibilities of interpretation opened by newer discoveries. Consequently I feel that the time has arrived when we should close our eyes and reflect upon the value of what we have seen, done and heard. If my re-analysis of hemodynamic fundamentals seems too elementary to some, or gratuitous to others, I beg their indulgence.

The Pulse Pressure and Pressure Pulse. During each ventricular systole a definite quantity of blood is ejected into the aorta. It is called the *pulse volume*, *stroke volume* or *systolic discharge*. In man, it averages about 62 cc. The interval of ejection is very short; about 0.25 second in man and less in lower animals. Moreover, the output is by no means constant during this period. Fully two-thirds of the total systolic discharge volume is displaced into the aorta in less than 0.1 second and very little is ejected during the last 0.05 second. Since the arteries are already fairly distended with blood at the moment when ejection begins additional room must be made quickly. This is accomplished partly by moving the column of blood onward (kinetic energy of flow), partly by distending the arterial walls and increasing the capacity of the arteries, i.e., it is stored as potential pressure energy.

The pressure changes thus created in the aorta can be recorded accurately in anesthetized animals by inserting a calibrated optical manometer through one of its branches. A typical curve is shown in Figure 1.

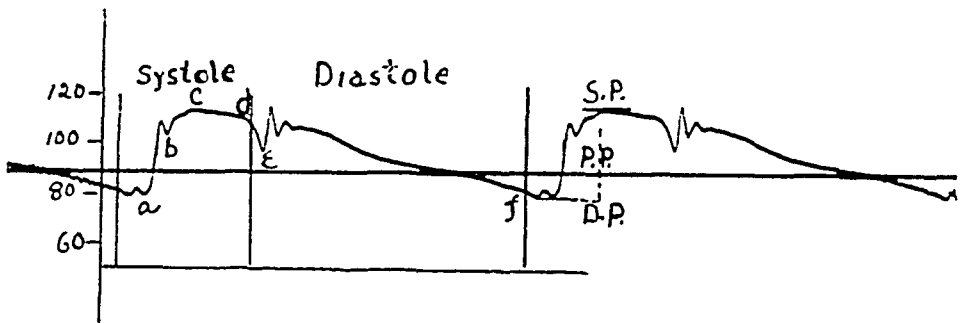


Fig. 1

For about 0.04 second after the onset of ejection (a-b), a great forward movement of blood together with a steep increase in pressure occurs. During the next 0.04 or 0.05 second (b-c), the pressure mounts with a slower gradient to a summit, but the velocity of flow decreases. During the remainder of systole (c-d), both pressure and flow gradually decrease together. The time of closure of the semilunar valves, demarcating the beginning of diastole, is accompanied by a sharp drop in pressure, the incisura (e). The pressure energy available at this moment is the effective force which gradually moves blood stored in the distended arteries through the arterioles into the capillaries during diastole. As conversion of pressure energy to flow occurs, the pressure curve slowly declines during diastole (e, f). Obviously, the conversion of potential energy stored during systole into kinetic energy of flow during diastole insures a reasonably continued flow through the capillaries where the interchange of foodstuffs, salts, water and gases goes on. Such pressure curves reveal also that the pressure in the aortic arch reaches a maximum during midsystole and a minimum at the end of diastole. These are referred to as *systolic* and *diastolic* pressures, respectively, and the numerical difference is called the *pulse pressure*.

The pressure values in mm. Hg at these moments of the cardiac cycle are the ones measured by sphygmomanometric methods in man and unanesthetized animals. Obviously, they give no information of the pressure changes between the points. The fact that arterial pressure readings taken by indirect methods only give information regarding pressures at two moments of the cardiac cycle must always be kept in mind in interpretations of clinical blood pressure readings.

The entire course of the pressure changes illustrated in Figure 1 and known as the *pressure pulses* can be ascertained in unanesthetized animals and man by two procedures:

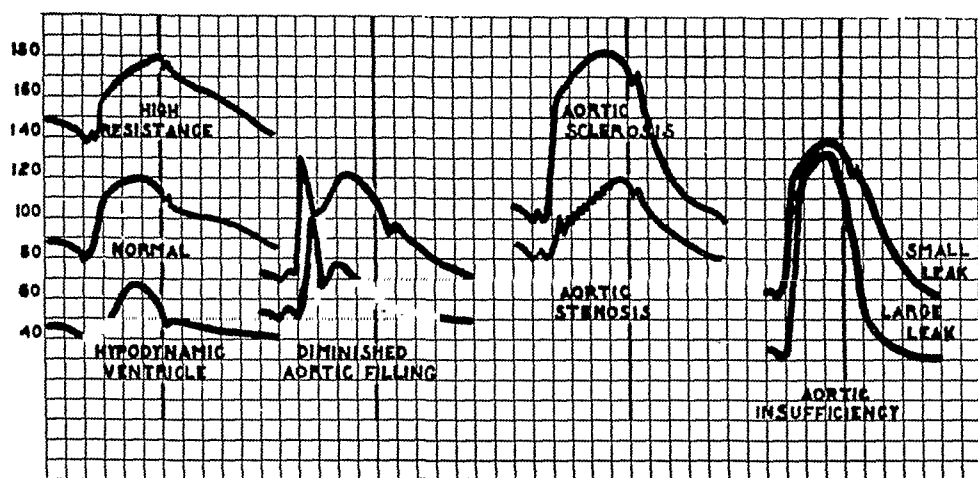


Fig. 2

1. They may be recorded by hypodermic optical manometers of the Hamilton or Gregg patterns. Unfortunately, hypodermic puncture of the subclavian artery is regarded as too hazardous; hence the cubital or radial arteries are more commonly used. Unfortunately, however, the form of the pressure pulse undergoes significant changes by the time it reaches the cubital artery. Their nature and causes cannot be considered tonight (cf. Wiggers²). For these reasons, the use of an otherwise admirable method is restricted to particular circumstances under which puncture of the subclavian artery seems warranted.

2. A simpler and harmless procedure, sufficiently accurate for most dynamic studies has been used by the author on patients.³ A cup is firmly pressed into the supraclavicular fossa of a patient in the sitting posture and a subclavian pulse recorded optically by a Frank segment capsule. Such a record gives the form but not the ordinate values of the pressure pulse. The latter can be supplied by determining systolic, diastolic and brachial pressures in the usual manner and placing them at the crest and trough points indicated in Figure 1. The intervening vertical distance can, if desired, be subdivided proportionally and the pressure value at any moment of the cycle thus established, much as in direct registration of pressures from the aorta in anesthetized animals by optical manometers.

The importance of a knowledge of the contour as well as the maximal and minimal values of pressure pulses in a number of common clinical diseases is illustrated by curves of Figure 2. Lesions of the aortic

valves produce particularly distinguishing features in the central arterial pulses. The pulse of aortic stenosis is characterized by a short sharp rise terminating in an anacrotic V-shaped notch or incisura. The greater the stenosis, the lower this notch. Following this, the pressure rises slowly to a maximum at the very end of systole; in other words, the pressure read as systolic is not that near midsystole as in normal states, but at the end of systole. Moreover, irregular vibrations are superimposed upon the basic form of the curve, thus furnishing a graphic inscription of the systolic murmur.

Analysis of aortic pressure pulses from experimental animals suggests that the central pulse contours in man can probably give information regarding the magnitude of aortic regurgitation. With large aortic valve leakage, the curves rise smartly to a rounded summit and decline appreciably during the latter part of systole. This is the *systolic collapse* which is interrupted by the deep incisura which follows immediately. The latter, continued during the early moments of isometric relaxation, constitutes the *early diastolic collapse*. During the remainder of diastole, pressure declines little, if at all. With smaller leakage of the aortic valves, the contour of the systolic portion is, on the contrary, not significantly altered. The early diastolic collapse is also not great, but the chief drop occurs during the latter portion of diastole. (For further discussion, cf. Wiggers.²)

During conditions in which the arterial system is not well filled, such as shock, hemorrhage, hyperthermia, the pressure curve rises to a sharp preliminary peak after which a lower and somewhat broader systolic summit is reached. Indeed, the question arises which of these peaks represents systolic pressure. This is of some importance since the differences may be as great as 50 mm. Since the first peak is due to a momentary overshooting in the lax arterial system, the midsystolic peak is the more reasonable index of systolic pressure, but auscultatory sphygmomanometer readings probably correspond to the former. The practical import of such discrepancies is that the systolic pressure of patients after hemorrhage or during shock appears higher than it actually is, therefore giving the false impression of a favorable prognosis. I have a suspicion that many clinical reports that systolic pressure can be high when a patient is in a serious state are due to too complete reliance on auscultatory readings, and an insufficient regard to the fact that the midsystolic pressure may be much lower, as shown in pressure pulses.

Factors affecting systolic and diastolic pressure. Since arterial pressures are determined by the degree to which the arterial walls are distended and placed under tension, *any factor that increases the volume of blood in the arterial tree increases pressures; and, vice versa, any influence that diminishes the arterial volume, reduces pressures.* This is so fundamental that it might be called the first law of hemodynamics. The primary variables affecting such arterial distension are the systolic discharge, the heart rate, and the peripheral resistance which is determined chiefly, but not wholly, by arteriolar constriction. However, increase in these three variables does not elevate systolic and diastolic pressures equally. Measurements of systolic and diastolic pressures, therefore, become most significant when their relative changes or the pulse pressure are evaluated. The effect of each influence acting separately has been predicted by mathematical considerations and theoretical analyses, taking into account the volume elasticity curves of the normal aorta. Thus, if the distensibility of the aorta be expressed as dp/dv and the volume of the aorta as V , then as long as $dp/dv \cdot V$ remains constant, the pulse pressure (dp) increases or decreases when either the systolic discharge (dv) or the capacity of the aorta (V) alters. When $dp/dv \cdot V$ is not constant, changes in pulse pressure are not easily predictable, but must be determined experimentally, with the aid of artificial models or animals. There is another reason why experimental studies are required to check mathematical predictions. The latter are generally based on the assumption that the volume of the aorta changes instantly at the beginning of systole and after closure of the semilunar valves. This does not occur in the body, as we have seen. However, on the whole, the results of experiments can be harmonized with theoretical considerations.

It can be shown by use of artificial circulation machines of proper design (cf. Wiggers^{2,3}): 1, that increasing the systolic discharge elevates systolic pressure more than diastolic, the pulse pressure being greater; 2, that acceleration of the heart raises diastolic pressure more than systolic, the pulse pressure being smaller; and 3, that augmenting the peripheral arteriolar resistance elevates diastolic pressure more than systolic, the pulse pressure decreasing.

The last of these dynamic postulates is apparently in conflict with the bulk of clinical observations on hypertension. As is well established, hypertension is also due predominately to an increase in peripheral resistance but almost invariably systolic pressure is increased more than

diastolic and the pulse pressure is larger. Even in so-called "high diastolic types" of hypertension the pulse pressure is never smaller than normal. In other words, hypertension is not wholly defined in a dynamic sense as an elevation of blood pressures, but as a disproportionately greater rise of systolic compared to diastolic pressure. As shown in Figure 2, the contour of the pressure fluctuations also deviates from the normal; the pressure rises abruptly during systole to a high level and the diastolic limb shows a rapid decline. Indeed, these features may be so pronounced that the pressure pulses somewhat resemble those of aortic insufficiency; the differences, of course, being that diastolic pressure is elevated in the former and depressed in the latter (Fig. 2).

The paradox that in dynamic models of the circulation an increase in peripheral resistance reduces pulse pressure, whereas in clinical and experimental hypertension a similar increase in resistance augments the pulse pressure has interested me for a number of years^{4,5} and led to considerable experimental work as well as recordings on patients in efforts to clarify the situation.

Evidence summarized elsewhere⁶ led to the conclusion that the larger pulse pressure in hypertension can only be explained by a concurrent decrease in the elasticity of the aorta. This fits with studies on a physical circulation model, for if, in addition to an increase in peripheral resistance, the aortic elasticity is reduced, systolic pressure rises still more while diastolic pressure decreases. This means, for example, that aortic sclerosis is unfavorable in increasing systolic, but favorable in reducing diastolic pressure. The pulse pressure obviously increases greatly and a condition of so-called "systolic hypertension" is created. Two important corollaries follow: 1, Aortic sclerosis or any other factor which reduces aortic distensibility accentuates the elevation of systolic pressure but tends to reduce diastolic pressure. 2, An essentially normal diastolic pressure in hypertension is not necessarily a favorable sign which indicates that peripheral resistance is normal. More often it denotes extension of a process to the larger arteries and particularly the aorta.

Nature seems to have provided a mechanism by which the dynamic effects of diminishing aortic distensibility, such as occur with advancing age, is at least partly compensated by an increase in the size or capacity of the aorta. Such an increase in size has the same effect on systolic and diastolic pressures as a decrease in systolic discharge would have with the diastolic size of the aorta unchanged. Either, if superimposed on a

primary vasoconstriction, tends to reduce the systolic pressure more than the diastolic.

There would seem to be no question but that arteriosclerotic changes discovered in the aorta at autopsy contribute to the high systolic pressures and account for the large pulse pressure in some cases of hypertension. But the aortic changes need not necessarily be due to visible morphological changes; they may not even be detectable in comparative determinations of volume elasticity coefficients of aortic cylinders or rings obtained at autopsy. On the contrary, there is increasing experimental evidence that aortic elasticity and capacity can change functionally. On the basis of studies on pulse velocities in central vessels, Böger and Wezler⁶ believed they had shown that aortic elasticity is greatly reduced, particularly in the so-called "red hypertension" of German clinicians. Personally, I have not been convinced that changes in pulse velocity are sufficiently accurate to allow such deductions.^{4, 5} But in experiments on normal dogs, Wégria and I⁷ were able to show that in acute hypertension initiated primarily by nervous and hormonal actions on peripheral arterioles, the initial passive expansion of the aorta is followed by an active diminution in size and, after a further latency, its elasticity is *increased*. In such experiments the effects of decreased size of the aorta overbalanced the opposing effects of an increased elasticity in raising systolic pressure. While we have no reason to conclude that these or similar conditions necessarily occur in clinical or experimental hypertension, they do stress the importance of functional changes in aortic capacity and elasticity as factors which determine the height to which systolic pressure rises.

To summarize, clinical and experimental hypertension is initiated by an increase in peripheral arteriolar resistance, but intensified as far as systolic pressure is concerned by functional or morphological changes in aortic capacity and/or elasticity. The cardiac output is only rarely increased, e.g., in cases of hypervolemia and thyrotoxicosis.

This aspect of hypertension complicates the interpretation of therapeutic claims made for agents which reduce blood pressure. The mere demonstration that a substance is capable of lowering systolic pressure is not tantamount to proof that this has been accomplished through abolition of the arteriolar constriction which initiated the high pressure. It has long been obvious that the high arterial pressure of hypertension can be reduced by drugs which cause an extreme slowing or depression

of the heart, a procedure which must be condemned as harmful as far as maintenance of a circulatory balance and adequate blood flow through tissues is concerned. That pressure reducing agents may also act on the aorta must at least be considered a possibility in view of newer evidence. If, by any chance, they should act by causing an extreme dilatation of the aorta, the value of such reduction of hypertension might be highly questionable. In short, it is not sufficient to establish therapeutically that drugs and various preparations reduce hypertension; it is even more important to know how they act. This would appear to be the next important step in the field of experimental work on hypertension.

Mean pressure. In experimental work, the lateral mean pressure in the aorta is commonly recorded by measuring the end-pressure in one of its accessible branches (e.g., carotid or femoral artery). This must be done by a properly damped Hg manometer, i.e., one in which the cardiac oscillations are barely discernible. Registration of wide fluctuations, as is still too common a practice among experimenters, renders readings of mean pressure inexact. The low period of Hg manometers prevents their recording either the systolic or diastolic pressure with exactness. The magnitude of error varies extremely under different conditions and the error may be opposite in direction at various times. For example, at very slow heart rates the momentum of the mercury column causes it to overshoot both during its ascent and descent, with the result that systolic pressure is recorded too high and diastolic pressure too low; on the contrary, at very rapid heart rates, the inertia of the mercury prevents full systolic and diastolic pressure from being reached, with the consequence that systolic pressures are recorded too low and diastolic pressures too high. All of these facts have been well-known since the introduction of the recording mercury manometer by Ludwig; but they seem to have escaped many experimenters who continue to speak of systolic pressure and pulse pressure thus recorded; hence this reiteration.

The mean pressure represents the average pressure during a succession of cardiac cycles and gives less explicit information than systolic and diastolic pressures. Owing to the form of the pressure pulse, it is never a mathematical average of systolic and diastolic pressures. As a matter of fact, a mean pressure is non-existent; but is a convenient fictitious value which has proved useful in hemodynamic considerations. Thus, it is commonly stated that as long as minute output of the heart

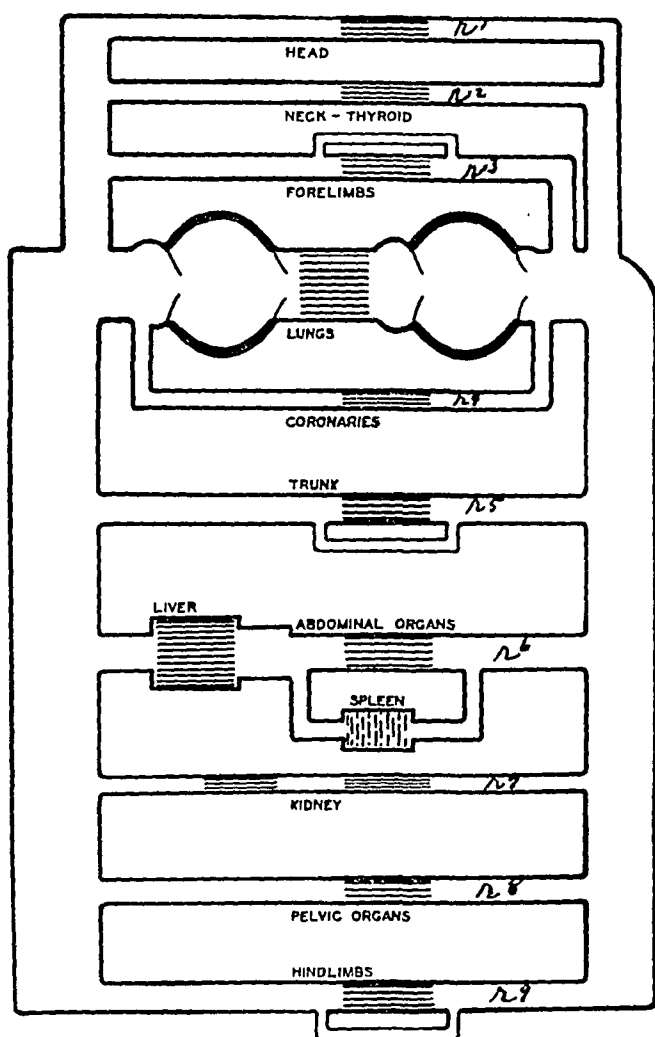


Fig. 3

does not change, any elevation of mean pressure denotes an increase, and a fall of mean pressure, a decrease in total resistance to runoff from the aorta, for changes in aortic elasticity do not affect the mean pressure. This resistance is due chiefly to friction in the various arterioles, capillaries and venules and to the additional resistance offered by venous pressures and viscosity of blood. As all students of hemodynamics are aware, the total peripheral resistance cannot be treated by regarding the circulation as having one resistance only. As shown in Fig. 3, it is composed rather of a series of parallel resistances, and, as in similar parallel resistances of an electric circuit, the *total resistance* is calculated as

$$1/R = 1/r_1 + 1/r_2 + 1/r_3 + 1/r_4 + \dots + 1/r_n.$$

A calculation of such a total resistance can be made in absolute units or it can be expressed as arbitrary units provided we know the mean pressure and rate of runoff, e.g., resistance = $\frac{\text{pressure}}{\text{rate of flow}}$. Since all of the blood ejected from the left ventricle during systole must leave the arterial system when mean pressure has reached an equilibrium, we can use cardiac output per minute or per second in such equations, as an index of rate of flow.

In this way, Frank, Böger and Wezler and others have used the formula

$$R = \frac{P_m \times 1332}{V_t} = \frac{\text{dynes. sec.}}{\text{cm.}^5} \quad (\text{absolute units}).$$

P_m denotes mean pressure in mm. Hg, 1332 represents a conversion factor to absolute units, and V_t represents the output per second. Resistances so measured range from 539 to 1150 absolute units in man, 2060—9080 A.U. in dogs and from 11,620 to 12,590 A.U. in rabbits. In other words, as might be expected with approximately equal mean pressures, the actual resistance varies inversely with the size of the animal, e.g., it is 11-13 times as great in rabbits as in man. For this reason, Bazett and associates⁸ found it advisable to introduce a factor for body size or sur-

face area and suggested the arbitrary formula $R = \frac{PM}{3 \sqrt{V_t/A}}$; in which A represents surface area, and V_t/A , the cardiac output index of Grollman. The factor "3" was arbitrarily introduced so that normal values in man would conveniently range around 100 (variations 79-138).

The use of such calculations may however contain a trap; if so, I have unwittingly fallen into it with other investigators in calculating peripheral resistance in patients with hypertension.⁴ Preliminary experiments on dogs reported in association with Dingle, Kent and Williams⁹ showed that when mean arterial pressure was increased to equal levels by reflex action, adrenalin, pituitrin, mechanical clamping of vessels, etc., the absolute resistances calculated from simultaneous records of cardiac output (oncometer) and mean pressure did not show the correspondence anticipated. Since Wégria and I had shown that such a rise in pressure is accompanied by a decrease in the capacity of the aorta, we suggested that this may be a factor which vitiates such calculations of total resistance.

If the magnitude of change in total peripheral resistance cannot be

evaluated quantitatively by such methods, there is still less chance that it can be inferred from variations in mean pressure, as is frequently done. Such inferences contain several sources of error. In the first place, any tyro in hemodynamics realizes that mean pressure cannot be used as an index of vasomotor power or peripheral resistance when the output of the heart changes simultaneously. However, the possibility of such changes in cardiac output are too often ignored, or it is assumed that they do not exist. The latter is a fallacy, for extensive observations on cardiac output by cardiometric registration has convinced me that pressor nerves or drugs which have no direct action on the heart generally do alter venous return and, secondarily, the cardiac output, in accordance with Starling's law. The sad fact remains that despite such knowledge, our best journals abound in reports, dealing with hypertension, shock and hemorrhage, localization and vitality of vasomotor centers, assay of drugs and hormones, etc., in which changes in mean pressure are used as a quantitative index of vasomotor power without controls of cardiac output.

However, assuming that reasonable proof is obtainable that changes in cardiac output are not significant, a second problem arises: Does the absolute or percentile change in mean pressure offer the better quantitative criterion of vasomotor power? In analyzing the observations that stimulation of pressor nerves generally causes less rise of pressure when the initial pressure is low than it does when it is normal, Porter¹⁰ in 1907 offered the following analogy: "An unfaithful trustee robs two women. One of these has \$40,000, the other \$20,000; from each he took \$10,000. Their absolute loss is the same, but one woman can still live on her income, while the other must work or beg." To this, Sollmann and Pilcher¹¹ retorted, "With the same absolute loss, the percentile loss of the two women is different, it is true; but the percentile gain of the trustee is the same in both cases. *A priori*, it is not clear whether the blood pressure is playing the role of the trustee or of the women." The questions thus started have never been settled. Our own efforts to do so failed when no consistent changes in calculated absolute resistances could be obtained. It remains for some genius in circulatory dynamics to find a way out of the present impasse. Attempts at statistical treatment, such as have been made, are, of course, no better than the value of the original data utilized. Finally, no one has even suggested a hemodynamic basis upon which absolute or percentile changes in *systolic*

pressure could serve as an index of vasomotor power. Nevertheless, even such studies have been made to test the relative potency of carotid sinus reflexes on the vascular system in normal and hypertensive subjects.

Investigators have, it is true, attempted to verify the existence of vasomotor changes by studying blood flow or volume changes in separate organs. The use of plethysmographs and oncometers constitutes a considerable advance when changes in a particular organ are concerned. Thus, when the mean pressure and volume of an organ alter in opposite directions, it usually denotes vasomotor change *in that organ*. Caution must, however, be observed in *extending* such interpretations. Changes in volume opposite in direction to blood pressure certainly do not mean that cardiac output is not concerned in the mean blood pressure changes obtained. This is obvious after injection of epinephrine, which generally causes an elevation of pressure and reduction in kidney size. The sampling of vasomotor reactions or vascular resistance in individual organs or the limbs—a common practice in studies on hypertension—is also not a safe index of the total resistance to aortic runoff from all of its branches. This is obvious from the formula in calculation of R . If r^1 or r^3 increases, a corresponding change in the opposite direction in r^2 or r^4 would leave R unaffected. Thus the demonstration that the rate of blood flow in the hands or arms is no greater than in hypertensive subjects does not prove that the high blood pressure is due to generalized constriction.

Demonstrated constriction in organs supplied by the mesenteric vessels can with more reason be accepted as leading to increased total resistance because the "splanchnic area" is dominant in affecting total peripheral resistance. It is possible, for example, to ligate all branches of the aortic arch—except the carotid arteries which start distorting sinus reflexes—as well as the descending aorta below the inferior mesenteric branch without causing elevation of aortic mean pressure or changes in calculated peripheral resistance. However, ligation of the superior mesenteric vessel, in addition, definitely increases both.

Résumé. Results of investigations on the circulation would be more concordant and the literature on the subject less confused if investigators and clinicians in general restricted their deductions and conclusions to those that are allowable on the basis of established fundamentals. The following principles were discussed:

1. The pressure variations created in the aorta by each discharge of

the left ventricle not only have a magnitude which is defined by readings of systolic and diastolic pressures, but a definite form which is manifested in optical records of the central arterial pulse. Significant changes in contour of importance in clinical conditions are graphically pictured in Figure 2, and briefly discussed.

2. Measurements of systolic and diastolic pressures only yield full information when their relative deviations, i.e., changes in pulse pressure, are considered. Dynamically, systolic pressure increases more than diastolic (pulse pressure larger) when the systolic discharge of the heart increases and when the capacity of distensibility of the aorta decreases. Diastolic pressure increases more than systolic (pulse pressure less), due to cardiac acceleration and increase in total peripheral resistance. Since a number of these reactions generally occur together in the body, their value in interpreting blood pressure changes has not proved as great as was at one time hoped.

3. Hypertension is not defined dynamically as an increase in blood pressure alone; the pulse pressure is always increased to varying degrees. This greater pulse pressure is generally due to decreased distensibility of the aorta and not to the increased peripheral resistance. There is reason to suspect that hypertension with little or no elevation of diastolic pressure is associated with a significant decrease in aortic elasticity.

4. Before agents which reduce blood pressure in clinical or experimental hypertension are acceptable therapeutically, it must be shown that they in fact reduce total peripheral resistance and that depressor reactions are not due to action on the heart or aorta.

5. Mean pressure is a fictional value which represents the mean of successive pressure changes in the aorta. It can fortunately be recorded directly by a highly damped mercury manometer. Writers should avoid erroneous statements or inferences that changes in pulse pressure can be gauged by such recordings.

6. The reciprocal of the total resistance is given mathematically by the sum of the reciprocals of resistances in parallel circuits of the arterial system. The resistance, calculated by the ratio $\frac{\text{mean pressure}}{\text{cardiac output}}$ increases progressively with body size, but the validity of such estimates is often reduced by the fact that possible changes in aortic capacity are not taken into account.

7. Elevations of mean arterial pressure can be attributed to changes

in total peripheral resistance only when it is proved simultaneously that the minute output of the heart or the capacity of the aorta has not changed actively. Since this does not happen under any circumstances known to the writer, changes in mean pressure, either absolute or percentile, cannot be used as a quantitative index of the intensity of arteriolar constriction or of the degree of activity of the vasomotor center.

8. The sampling of vasomotor reactions or vascular resistance in individual organs or limbs—a common practice in studies on hypertension—does not allow the conclusion that total peripheral resistance is increased or that such increase is the chief cause of the hypertension.

9. Finally, the themes are stressed that experimental results are no better than the apparatus employed, that the analysis of dubious results cannot be improved by statistical methods, and that the breadth of conclusions drawn should not exceed the limitations permitted by the most accurate results.

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HEART FAILURE*

The Wesley M. Carpenter Lecture

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“A CERTAIN man became very breathless and grew thin. All observers blamed the lungs. When the cadaver was opened nothing remarkable was found in the lungs, but the heart, mirabile dictu, equalled the size of a large head; it was so large that it contained all the blood and spirit.” This case cited by Ballonius and published by Theophilus Bonetus in the first edition of the *Sepulchretum* in 1679 was, so far as I know, the earliest instance recorded of the association of enlargement of the heart, that is, of heart disease, with dyspnea doubtless due to heart failure.

“A very fat poet who for a long time had suffered from asthma and frequency of urination and for some little time also from dull pain in the left side, spent a convivial evening at dinner with friends and relatives reciting to them all manner of odes, both hilarious and sad, including even a funeral lamentation. At nine o’clock he rose from his seat and as he made the effort of mounting the stairs he was seized with an increasing difficulty in drawing his breath. Aided by his secretary, with great effort he reached his couch, reclined, accepted absolution, and expired. The next day when his abdomen was opened, everything was found loaded with fat. His abdominal wall measured three fingers in thickness and his omentum easily weighed 30 civil pounds. The liver and spleen were large, the bladder small and weak. The heart was rather large and the coronary blood vessels were unexpectedly and extensively bony with thin membranes covering the bone on both sides, and in two places the bony walls were so completely contiguous that not even the point of a fine needle could enter. The lungs were large.”

This case cited by Bonetus himself and published in the second edition of the *Sepulchretum* in 1700 was, to the best of my knowledge, the first recorded instance of the association of rapid death with a high de-

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gree of coronary disease, quite probably a fatality from coronary occlusion. It antedates Heberden, Jenner, and Parry by nearly a hundred years, and although casually referred to by Morgagni in 1761, has apparently escaped the notice of the generations that have followed.

The fact that the recognition of these serious end results of heart disease came so slowly, and not until the Seventeenth and Eighteenth centuries, is of course to be ascribed to the rarity of autopsies in earlier days, to the cursory examination of the viscera in those that were done, and to neglect of good history taking. But to think that the essence of knowledge about these things is new in our own generation is an error and unfair to those who have gone before us. "Men were not all cowards before Agamemnon or all fools before the days of Virchow and Billroth." Because of the general ignorance about the valuable cardiovascular contributions of some of the medical leaders of their day, two or three centuries ago, and because these contributions sum up the essence of our present day knowledge of the mechanism and symptomatology of the congestive phenomena of heart disease, I shall take a few minutes to give you some pertinent quotations.

Even before the *Sepulchretum* of Bonetus, Richard Lower, who was the first to transfuse blood by tubes from one animal to another, wrote in 1669 of experimental compression of arteries and veins with the resultant congestion; he also described constriction of the heart in man by pericardial effusion and by a thick and hard pericardium.

In 1715 Vieussens described very well a case of mitral stenosis. He added the following observation. "The opening of the auricle into the ventricle was so stenosed that the blood could no longer freely enter. The circulation was, therefore, so embarrassed that it began to cause an extraordinary dilatation of the pulmonary veins and retarded the passage of blood through all the vessels of the lungs, which became so engorged that they compressed the air vesicles and hindered the free entrance and exit of air to and from them; which explains why the patient always breathed with difficulty."

Vieussens also wrote of acute and chronic pericardial constriction of the heart, diagnosing correctly one of the acute cases. Incidentally he described the waterhammer or Corrigan pulse in a patient with aortic regurgitation.

But it was Lancisi, remarkable physician to Pope Clement XI in Rome, who deserves the most credit for analyzing the sequence of events

leading to heart failure. On page 136 of his book, *De Motu Cordis et Aneurysmatibus*, published posthumously in 1728, it is stated that obstruction to the course of blood either in the heart or in the major vessels is obviously a cause of enlargement of heart and blood vessels, most readily of the auricles and veins because of their thin walls. He cited on the next page the case of a clergyman of St. Peter's at the Vatican who was troubled by suffocative asthma and vertigo and who showed at autopsy calcareous aortic stenosis and cardiac enlargement. He added the significant statement that the strenuosity of this clergyman's body and mind was such as to cause an increased blood flow with so rapid a return of blood to the heart that heart chambers, lungs, and veins were overfilled, ample reason, he said, for the dyspnea and enlargement of the right heart chambers. Thus Lancisi presented an exciting or secondary factor, as well as an organic or primary one. Furthermore on page 141 Lancisi added the following remarks: "From dilatation of the right auricle and ventricle two results develop which cause dilatation of the jugular veins and are worthy of the greatest consideration. The first of these is the overfilling of the right heart chambers and hence the jugulars with blood. The second is the insufficiency of the tricuspid valve due to the dilatation of the right heart chambers, which insufficiency allows the transmission of the pulsation of the ventricle backward into the right auricle and venae cavae as well as forward into the pulmonary artery." This he called a new sign ignored by earlier authors, partly because it was not noted post mortem.

Senac and Morgagni followed suit, the former in 1749, the latter in 1761. Senac emphasized, as Lancisi had not done, that even the stout, thick-walled left ventricle might be dilated and enlarged, as he found it to be in a case of aortic stenosis. "If the left ventricle," said he, "must dilate when it cannot empty itself, the dilatation then must involve even more its auricle and the pulmonary veins." Of Lancisi's case he wrote: "The blood was arrested in the lung, hence the asthma and the dilatation of the right ventricle, its auricle and the vena cava." He also wrote of the finding of edema of the feet in some cardiac cases, and of hydrothorax.

Morgagni spoke of the slow course of the heart failure in some cases and he too described the sequence of events in a young man with aortic regurgitation. "You will perhaps ask," he said, "why, as all the four cavities of the heart were dilated in the young man in question the dila-

ration of the left ventricle was, nevertheless, the greatest? Without doubt, because the dilatation of the ventricle had given rise to the dilatation of the other ventricle and the two auricles; that is, by admitting a less quantity of blood than it ought, for the reason which I just now gave you; and, in consequence of this obstruction, by retarding the motion of the blood in the left auricle, in the lungs, in the right ventricle, and its adjoining auricle. But why was the left ventricle the first of all to be dilated? Why, certainly, because the semilunar valves, whatever the cause of this circumstance might be, having been contracted and corrugated, could not properly expand themselves, so as to prevent the blood from being, in part, sent back into the ventricle, from whence it came."

One more historical reference to wind up the important but much neglected statement of the debt we owe our forbears for ideas about heart failure. Hope's writings are much better known and date back to only a little over a hundred years ago (1832) but they are so clear and additionally helpful that they are worth quoting in brief. "As an obstacle to the circulation operates on the heart in a retrograde direction, the cavity situated immediately behind it is the first to suffer from its influence. Accordingly all the impediments seated in the aorta, its mouth, or the arterial system, act primarily on the left ventricle, which being likewise exposed to the heaviest burden when the circulation is accelerated, has to conflict against a greater variety of exciting causes of hypertrophy, than any other cavity of the heart. . . .

"So long as the left ventricle is capable of propelling its contents, the corresponding auricle, being protected by its valve, remains secure. Hence, in a large majority of cases, the auricle is perfectly exempt from disease, while the ventricle is even enormously thickened and dilated. But when the distending pressure of the blood preponderates over the power of the ventricle, its contents, from not being duly expelled, constitute an obstacle to the transmission of the auricular blood. Hence the auricle becomes overdistended and the obstruction may be propagated backwards through the lungs to the right side of the heart, and there occasion the same series of phenomena. . . .

"When the mitral orifice is contracted, especially if the aperture be very small. . . . the left auricle, having to struggle against the contracted valve in front, and also to sustain the distending pressure of the blood flowing in from the lungs, invariably becomes thickened and di-

lated. The engorgement, extending backwards through the lungs to the right ventricle, occasions its hypertrophy and dilatation; under which circumstances, namely, hypertrophy of the right ventricle and contraction of the mitral valve, the lungs suffer in a preëminent degree (as said Vieussens a hundred years earlier); for, being exposed to the augmented impulsive power of the right ventricle behind, and incapable of unloading themselves on account of the straitened orifice in front, their delicate and ill-supported vessels are strained beyond the power of resistance. . . .

"When the impediment to the circulation is primitively seated in the lungs, the right ventricle, situated immediately behind them, is the first to experience its influence. . . .

"The primary effect of universal obstruction of the lungs by engorgement, is, to produce oedema of their cellular tissue and dyspnoea; whether the latter depends solely on the engorgement or *partly also on spasm of the bronchi excited by the irritation of that congestion* (italics, mine), is difficult positively to determine, though the latter is highly probable. . . . The secondary effect is, to gorge the right side of the heart, and thus impede the return of the venous blood from the system at large; which cooperates with the increased energy of the arterial circulation in producing anasarca."

Why was it that these evidences of heart strain and heart failure were discovered so near the beginning of any knowledge of heart disease, two centuries or more ago? Because they are of course such gross and often terminal conditions that they naturally could not help but excite speculation before death and interest in the findings post mortem. There was nothing delicate or mysterious about the situation except in some of the details which have been so well elucidated by many authorities in a resurgence of interest in heart failure in our own generation. I do, however, even while recognizing the need of ample knowledge of this very subject, protest against such an observation as that made by Lewis on page 1 of both editions of his book on heart disease, namely, "The very essence of cardiovascular practice is recognition of early heart failure and discrimination between different grades of failure." I admit that it is necessary to diagnose and to treat heart failure when it comes, but I am sure that we should regard this task as of minor importance compared to both the search for the presence of heart disease before failure comes, and the recognition of the fundamental causes

of heart disease even before the heart has become affected or at least seriously involved. To be sure we can't always do much to combat these factors as yet or to prevent or delay heart failure, but often we can do something, and in that direction obviously lies the hope of the future. I dare say we shall always have victims of heart failure among us, but if such failure can be limited or postponed to old age we may feel that we have accomplished much. Of greater importance than the diagnosis and treatment of heart failure are studies of the causes of heart disease and of its presence before the heart fails.

Before proceeding further it is wise for me to define a little what we mean by "heart failure" as a term in common use and as already illustrated by the historical quotations I have given you. When death comes, the heart stops beating, no matter what disease is fundamentally the cause of the death. But that is not what we mean by heart failure unless heart disease is the essential cause. The heart may suffer from the toxicity of infection or from disease of other organs such as kidneys or thyroid gland, but only rarely to the degree of being responsible for failure; rheumatic fever and diphtheria are among the rare exceptions to that statement. Nor do we label as heart failure the results of hemorrhage or traumatic or vascular shock when, from decrease of circulating blood or vasomotor paresis, the heart receives too little blood to keep up the vital circulation to brain and elsewhere. This is circulatory but not heart failure, though the one on occasion may excite the other.

Nor do we ordinarily label as heart failure conditions in which the fault lies in the inability of the heart to maintain an adequate supply of blood to the arteries, capillaries, and tissues of the body because of some abnormality of the heart structure itself or of its mechanism while the myocardium remains strong. To be sure such trouble is due to failure of the heart itself to "deliver the goods" and might well be called a type of heart failure. In fact it has sometimes been labelled "forward heart failure" in contrast to congestive heart failure, and it is perfectly reasonable to regard it as such. Incidentally the causative factors may lead to congestive failure in its turn.

Those factors which cut down the output of blood into the arterial system, either with or without congestive phenomena essential to them, are as follows. First, those that need not be attended by congestion are aortic stenosis, excessive heart rates in paroxysmal tachycardia, and high

grade sinoauricular or auriculoventricular heart block, conditions that may lead to syncope and even to death, as when aortic stenosis sufficiently cuts down the coronary circulation in middle age or later, when ventricular tachycardia fades into ventricular fibrillation, or when ventricular standstill lasts more than a few seconds. Second are those obstructive states that are attended by both limited output of blood and congestive phenomena, without necessarily any muscle weakness or failure, namely, mitral stenosis, tricuspid stenosis, and constrictive pericarditis, acute and chronic; in these conditions the congestive phenomena are generally much more prominent than the effects of a limited blood supply to the arteries and arterioles and it is, therefore, this very group that is often mistaken for congestive heart muscle failure. Third is myocardial failure itself which is also attended preponderantly by congestive phenomena.

Finally, there is still one more set of cardiac abnormalities responsible for inability or failure of the heart to maintain an effective circulation, namely, various congenital defects. One of the most striking of these is the large auricular septal opening which causes the right heart chambers and pulmonary circulation to be overloaded with blood and hence congested without myocardial failure. Another anomaly acts just reversely to deprive the pulmonary circulation of blood and to overload the aorta and systemic circulation with poorly aerated blood, namely, the tetralogy of Fallot with its pulmonary stenosis, ventricular septal defect, and dextroposition of the aorta. A patent ductus arteriosus puts a burden of variable degree on both sides of the heart but this is usually not great and rarely leads to heart failure per se. Some of the extreme congenital anomalies result in death in early infancy due to the impossibility of the maintenance of an adequate circulation to the body as a whole and not necessarily to heart failure itself.

Having thus presented a large group of conditions in which the heart is structurally or functionally unsuccessful in maintaining a proper circulation, but in most of which the myocardium itself is clinically sound, we come to the two major types of heart failure as they are popularly known, namely, myocardial or congestive failure, and coronary insufficiency or coronary failure. The latter is fundamentally a vascular disease but since the coronary arteries are practically a part of the heart's structure, their serious involvement with resulting inadequate blood supply to the heart muscle, can justifiably be accounted a type of heart disease and of heart

failure, called by Lewis and others the anginal type in contrast to the congestive type. Let us consider this coronary species of heart failure first, leaving for the end the kind that is more commonly thought of by the medical profession when heart failure is mentioned. Failure of the myocardium to receive an adequate blood supply is as a rule first shown by the symptom of angina pectoris and by characteristic electrocardiographic changes on effort. If the coronary circulation is blocked by a thrombus, then the pain (the status anginosus) lasts for hours, until the affected bit of heart muscle dies, while the electrocardiographic changes develop more extensively and last for days or weeks or even permanently. Recovery may be complete or death may come suddenly, even in the very first attack of angina pectoris, due probably to the development of ventricular fibrillation. Such a death is sometimes a just basis for the term sudden death from heart failure. Or, anginal failure may evolve after myocardial infarction or when superimposed on another kind of heart disease, hypertensive, for example, into considerable cardiac enlargement and congestive failure. But heart failure of the coronary type is evidenced only by angina pectoris or characteristic electrocardiographic abnormalities, and not by its various complications, including even death itself which cannot be called coronary with certainty without the presence of one or the other manifestation just mentioned. It is reasonable, however, to assume that a person who dies suddenly after recurrent attacks of angina pectoris has died a "coronary heart failure" death.

Now let us turn to congestive heart muscle failure about which the early authorities wrote and which is what we mean in the great majority of cases when we use the unqualified expression "heart failure." I want to emphasize a few important points about the causes, manifestations, diagnosis, and treatment of heart failure based largely on my clinical experience of the last two decades. Myocardial failure may be quite rapid in its development but it is usually slow and often insidious, though discernible if adequately sought for in an early and slight stage; it is never instantaneous as is the case with heart failure of the anginal type. It is always preceded by obvious cardiac enlargement; hence when dyspnea and edema are found with a heart of normal size they cannot be ascribed to heart muscle failure but must be credited to other causes of congestion. Heart muscle failure may begin on the left side or on the right side, or, least commonly on both sides of the heart simultaneously.

The factors responsible for heart muscle failure are almost as numerous as the causes of heart disease itself. They are best divided into primary and secondary factors. Sometimes multiple factors are responsible in a given case. Rarely the cause is unknown or undiscoverable.

Drs. Boyer, Leach, and I analyzed two years ago the primary and secondary factors responsible for congestive heart failure in 1000 cases, 500 from the wards of the Massachusetts General Hospital and 500 seen in private practice. Our experience will naturally differ somewhat from that of others who live where rheumatic fever is less common and syphilis or anemia more common, or who are pediatricians with the rheumatic group making up almost the total percentage. Actually we found that in our group hypertension as an underlying strain, with or without coronary heart disease, topped the list with a total of 47 per cent, rheumatic heart disease was second with 26 per cent, and uncomplicated coronary heart disease, that is, uncomplicated except by myocardial infarction, was third with 16 per cent. No other factor was responsible for as much as 5 per cent. Lues, for example, accounted for but 3 per cent, the cor pulmonale for 2 and congenital defects for only 1. Four per cent were of unknown origin. Males outnumbered females about two to one in the entire group of 1,000 cases.

Of even more interest were our findings with respect to precipitating factors superimposed on the underlying causes to set off the failure. Auricular fibrillation led the list of the recognizable complications, being clearly responsible for 14 per cent, doubtless due to the associated tachycardia. Coronary thrombosis, to our surprise, was second, being the exciting factor in 13 per cent. Respiratory infections were third with 11 per cent. Rheumatic fever was the obvious cause in 7 per cent. Pulmonary infarction was the factor in 3 per cent, malignant hypertension in 2, exertion in only $1\frac{1}{2}$, anemia in 1, and thyrotoxicosis in but 0.7 per cent. In a large group of 38 per cent the onset was very gradual with ill-defined or no precipitating factor, quite likely some very minor strain setting off the failure in the case of a myocardium whose reserve was nil; in 5 per cent the onset was very sudden due also to unknown precipitating factor. In only five cases of the thousand could a surgical operation be blamed for the failure. Pregnancy was the precipitating factor in two patients. Trauma was responsible in two and excessive ingestion of fluid in one.

To attempt to discover and appraise the precipitating factor in con-

gestive heart failure is decidedly worth while since we found that "when failure is precipitated by a removable or controllable cause, such as auricular fibrillation, respiratory infection, exertion, and thyrotoxicosis, the patient has roughly a 50-50 chance of regaining some degree of compensation. This is also true of those patients in whom failure occurred suddenly with no assignable cause and it seems likely that here, too, some temporary factor was at work." The prognosis, we found, depended much more on the exciting than on the underlying causes or on the age of the patients, except that those over seventy did poorly. Marked cardiac enlargement carried with it a poor prognosis, regardless of cause. Hypertension was a hazard, increasing the incidence of heart failure in patients with myocardial infarction.

It is, of course, of prime importance, in appraising a case, to determine not only the particular underlying and precipitating factors but to decide and state clearly the degree of structural change from the normal and the severity of the exciting cause. Thus, rheumatic heart disease may be slight with minimal strain from any respiratory infection, never reaching the limit of the cardiac reserve over a long life. On the other hand, extensive myocardial infarction complicating hypertensive heart disease may lead to rapid failure and death. Between these two extremes all grades of strain result in all grades of cardiac enlargement and failure. Some hearts remain competent for many years despite constant strain.

What are the evidences of myocardial failure and what are other conditions that may simulate it? Since at least three-quarters of all cases of myocardial strain have such strain exerted on the left ventricle as the result of systemic hypertension, aortic valve disease, or myocardial infarction, the first evidence of such strain is left ventricular enlargement, and the first symptom to show that the strain is proving to be serious enough to cause pulmonary vascular congestion is breathlessness on effort that had previously not been elicited by that particular effort and which cannot be blamed on some complication like a bronchial infection. The interval of time between the beginning of the development of cardiac enlargement and the onset of this symptom of dyspnea varies from hours in the case of a fulminating large myocardial infarct to a good many years in the case of a slowly progressive systemic hypertension or aortic stenosis. But enlargement there must always be, due to dilatation or to dilatation and hypertrophy, before dyspnea can rightly be

attributed to heart failure. The non-cardiac causes of dyspnea are more numerous than the cardiac and may be wholly responsible even in a cardiac patient, but it is a common experience to find that a non-cardiac cause may itself precipitate failure of the heart, particularly a respiratory infection in winter in an old person with heart disease; in such cases one must use a good deal of skill in determining how much of the dyspnea may be due to the heart and how much to the complicating respiratory infection—special tests of blood-flow velocity can help here.

The dyspnea in mitral stenosis is to be differentiated from that in the case of left ventricular strain and failure from the standpoint of pathogenesis, prognosis, and treatment. As Vieussens indicated so clearly over 200 years ago, this dyspnea is not to be ascribed to heart muscle failure, though it often leads to it, but then of the right ventricle and not of the left. It is common for severe dyspnea, even to the point of acute pulmonary edema, to develop suddenly in a patient with mitral stenosis who had previously been doing well, due to the onset of auricular fibrillation which so often complicates mitral stenosis. The tachycardia, which practically always accompanies auricular fibrillation at first, overloads the lungs with blood and increases pulmonary arterial pressure to the point frequently of causing the right ventricle to fail in its turn; hence it is quite obvious why the error of ascribing the dyspnea in mitral stenosis to heart muscle failure is so often made. There is certainly a failure in the cardiac mechanism but not of the myocardium *per se*. Fortunately, digitalis which is the drug *par excellence* for congestive heart failure helps tremendously in these cases by reduction of the heart rate by producing heart block and so relieves the strain on both the pulmonary circulation and the right ventricle.

Dyspnea on effort as the first evidence of congestive heart failure in most cases usually tends to increase without treatment and may eventually be present even at rest, resulting in orthopnea, and often in emphysema; and it sometimes is complicated by asthma, which, as Hope so well pointed out, is a superadded reflex phenomenon, to be called in these cases "cardiac asthma" but not to be considered an essential result of left ventricular failure, even in acute stages. Rarely does the pulmonary edema reach the stage of blood spitting. There may be some blood-stained sputum in the most severe acute cases, but if blood is raised in quantity, it almost invariably comes from pulmonary infarct or infection, the former of which so often complicates congestive heart failure.

Signs of left ventricular insufficiency or failure are somewhat slower to develop than the dyspnea on effort. By the time they appear the condition is fairly far advanced. They include accentuation of the pulmonary second sound, which may in hypertensive cases even equal or surpass the already accentuated aortic second sound, diminution of the first sound, and protodiastolic gallop rhythm at the apex. It is important to note that the gallop may be seen or felt even better than it is heard. There may or may not be a mitral systolic murmur due to mitral valve dilatation; other older murmurs, for example, that of aortic stenosis may be strikingly decreased. The pulsus alternans is a fairly common sign of left ventricular weakness but it is usually not looked for. Roentgen examination in advanced cases shows dilatation of the pulmonary artery and its branches in the lung hiluses and in very serious cases it may reveal pulmonary edema; it may incidentally demonstrate the important and common complication of pulmonary infarction, though such is much more frequent after the right heart fails. Incidentally, rales at the lung bases are an *advanced* sign of pulmonary edema and are much more often due, in my experience, to pulmonary infection, or to unilateral or bilateral infarction, or even to atelectasis.

Cyanosis may result from pulmonary congestion when left ventricular failure is of high degree, but is also to be found when right ventricular failure causes stasis, and indeed without any myocardial failure at all when the lungs are seriously congested in mitral stenosis or otherwise, or when there is local systemic venous stasis due to a local circulatory fault. Many patients with congestive heart failure have no cyanosis at all, except terminally.

Let us turn now to evidence of failure of the right ventricle which most often follows that of the left side, but which may result from mitral stenosis or pulmonary vascular disease without left ventricular strain or failure. Probably the very first evidence, if we look for it, is to be found in engorgement of the liver. The liver can doubtless soak up quite a little blood before the venous pressure is much, if any, elevated or enough to be clearly evident by inspection of neck veins or by elevation of actual pressure readings above the rather wide normal range. Dr. Boyer and I have found, for example, that a very early symptom of right ventricular insufficiency in mitral stenosis is *right upper quadrant abdominal pain on effort*, due doubtless to acute hepatic engorgement, comparable to the acute pulmonary engorgement which causes dyspnea

on effort relatively early in the case of left ventricular sufficiency.

Acute and subacute engorgement of the liver that lasts for days or weeks is common and can be readily recognized because of the combination of hepatic enlargement and tenderness in the case of a patient with serious strain of the right ventricle or with very severe acute rheumatic involvement in early childhood. It may subside quickly or slowly with rest and drug therapy but it may go on to a permanent state of liver congestion lasting for years. Chronic enlargement is most common in cases of mitral stenosis and chronic constrictive pericarditis and in such patients may eventually lead to a variable, though rarely extreme, degree of cirrhosis, justifiably called cardiac cirrhosis of the liver, but different from Laennec's, although not long ago it was suspected (but not proved) that some or all of the cirrhosis in rheumatic heart cases might be the result of an acute rheumatic hepatitis. It is natural that the liver rather than the systemic veins should bear the brunt of evidence of right ventricular failure or constriction, and show congestion earlier and often more severely, because of the low pressure in the portal and hepatic circulation and because of the angularity of the entrance of the hepatic veins into the inferior vena cava (along with the effect of gravity).

There are two other points of particular interest concerning the liver in congestive heart failure. The first concerns its pulsation. It used to be thought that a vigorous liver pulse indicated tricuspid valve disease with stenosis; Mackenzie was one of several who exploded that idea. It may, to be sure, and in fact often does, accompany tricuspid valve disease with regurgitation, but when well marked it is of course due to tricuspid regurgitation whether the valve itself is damaged or not. In fact it is now recognized that irreversible dilatation of the tricuspid ring, chiefly in cases of severe mitral stenosis, with little or no tricuspid valve deformity, may remain after recovery, in whole or in large part, of the right ventricular myocardium from a state of congestive failure; this circumstance is well and probably best shown by vigorous systolic pulsation of the deep jugular veins. The liver may pulsate whether or not the heart rhythm is normal, but auricular fibrillation is most often found in such cases and then the liver pulse is a single wave, the ventricular type, as Mackenzie used to call it. Undoubtedly the liver actually pulsates in most cases but in a degree that cannot clinically be recognized in the majority.

The other important observation about the congested liver is that

when a large pulmonary infarct is superimposed, as not rarely happens, there appears a jaundice usually of slight degree, but once in a while more pronounced, due to the inability of the congested liver to take care of the hemolyzed blood pigment from the infarct; and this may cause undue concern about the biliary tract. Such jaundice is always an important sign, however, and if pronounced, is serious.

Next in importance as a sign of right ventricular failure or constriction or of irreversible dilatation of the tricuspid valve or tricuspid valve disease is increased pressure and pulsation in the systemic veins, best noted in the jugulars but occasionally widespread over the body. In cases where the systolic pulsation is marked, there is a very appreciable pulse pressure in the larger veins, consisting in the neck for instance of several centimeters between systole and diastole. The more the engorgement, the less the visible pulsation; hence in most cases of congestive failure the venous pulse is much better seen with the patient upright than in the recumbent position. One other observation about the venous pulse is of special interest and that is the occasional error that may be made in confusing the deep systolic jugular pulse, that actually raises the sternocleidomastoid muscle, with a vigorous carotid pulse. It is easy to avoid this error by observing the sustained character of the venous (c plus v waves) in contrast to the arterial pulse, and by its easy obliteration by relatively light pressure over the jugular bulb. The possibility of this error was pointed out many years ago by Lancisi and, later, by Mackenzie, but is not yet recognized by the large majority of medical observers.

The third sign of right ventricular failure or constriction is dependent edema, of the feet and legs in the upright position, of the lower back and abdominal wall when supine, and of arm and even thorax and one side of the face when lying on one side. Its degree varies tremendously not only with the degree of hydrostatic pressure secondary to the failure of the heart but also with the presence of complicating factors, the most common of which are local obstruction to the venous flow as in cases of varicose veins and thrombophlebitis, and hypoproteinemia in cases of malnutrition. In fact, in some patients without any heart disease at all these other conditions are confused carelessly with congestive heart failure and treated by giving digitalis; in my experience local venous obstruction is often so misinterpreted, malnutrition rarely. Nephrotic edema is also rarely confused with congestive heart failure.

Hydrothorax is an occasional congestive phenomenon in right heart

failure, not in left, and it happens that it is almost invariably right sided at first or entirely. If there is isolated or preponderant left hydrothorax one should look for a complicating factor of pulmonary and pleural infarction or infection; in fact, such may be a hidden cause even in cases of congestive heart failure with right or bilateral hydrothorax.

Ascites is also an occasional congestive phenomenon, usually in advanced dropsy, but also in cases of chronic constrictive pericarditis and mitral stenosis in which the portal circulation has been long obstructed. In some cases of the former condition, that is, constrictive pericarditis, there may be in the subacute or transitional stage an actual peritonitis as a part of the polyserositis, and responsible for some, at least, of the ascites; in most cases, however, there is no peritonitis to give rise to ascites or frosting of the liver—in such patients, the portal obstruction is wholly responsible for the ascites.

One other sign of right ventricular weakness and failure which has been inadequately referred to except by the French school is a diastolic gallop rhythm, maximal not at the apex, as in the case of left ventricular weakness, but over the main body of the right ventricle and so best noted at the left of the midsternum. The most striking instance of this sort that I have ever encountered was in a patient with chronic constrictive pericarditis whom we recently found in a greatly improved state a few months after pericardial resection. His right ventricle had been decorticated and was seen to be beating directly under the skin and soft chest wall tissues (the ribs had been removed over it). It was still obviously atonic and flaccid in diastole, although the systolic retraction seemed fairly vigorous. There was a marked protodiastolic gallop, much better felt and seen than heard, a circumstance commonly found in gallop rhythm but not to the degree noted in this particular patient.

By fluoroscope in right heart failure the superior vena cava may be seen to be engorged and pulsating, but this is not important, for in such cases the jugular pulse is easily detected anyway.

What can we say about other evidences of or tests for congestive heart failure? Help from the x-ray I have already mentioned: There is always a large heart and the size may or may not materially change under observation, growing larger during the failure and smaller again when the myocardium has recovered its tone; in failure of the left ventricle engorgement of the pulmonary circulation is an important sign

and evidence of this in dilated pulmonary arc and lung hilus shadows is one of the chief reasons why roentgenology is a very useful adjunct in the study of heart disease; we don't need its help when the right ventricle fails.

Electrocardiography affords us little or no information of value in congestive heart failure except to tell us which ventricle may have been preponderantly under strain previously and to aid in following digitalis therapy; the prolongation of systole, as measured electrocardiographically, if it really occurs at all in congestive heart failure, is so slight as to be unimportant.

The estimation of the vital capacity of the lungs is not very important; it gives us, however, something of a quantitative figure in following the progress of an individual case which may be quite evident by clinical inspection. For diagnosis it must be interpreted with great caution because of the various other conditions besides congestive heart failure which may affect it.

Studies of the velocity of blood flow are also usually unnecessary, but they do have a place in doubtful cases, for example, in helping to decide whether dyspnea and asthma are due to left ventricular failure or to pulmonary disease or bronchiolar constriction; there will be a delay in all the tests from venous to arterial circulation if congestive failure is responsible for symptoms and signs.

Blood and urine examinations are not important except to reveal the degree of anemia that may be an exciting factor of heart failure, or the presence of leukocytosis in the case of suspected complication of infarction or infection, or of hypoproteinemia as a factor in the causation of edema, or urinary findings of renal disease. Albuminuria is, however, a common, in fact usual, accompaniment of congestive failure of the right ventricle.

I would add a brief word about fever before leaving the subject of diagnosis. It is quite likely that a slight rise of rectal temperature above normal, up to a degree or a trifle more, may occur in congestive failure of the right ventricle because of the difficulty in dissipation of heat from the edematous body with its faulty circulation, but any appreciable fever is to be attributed always to some important complication generally in the form of infarction (particularly pulmonary), or infection (particularly pulmonary or acute rheumatism). Dr. Kinsey and I found that every one of fifty consecutive cases of congestive failure that came

to autopsy showed at least one complication that could account completely for the fever that had been present often for some time before death, although during life it was often difficult or impossible to prove the presence of any such complications. Also it was apparent that the complication was the last straw, none of those fifty patients dying of the congestive failure alone.

What is the prognosis of congestive heart failure? Usually bad, if failure of either ventricle is easily diagnosed and not rapidly cleared after the subsidence of some excessive strain such as a very rapid heart rate in auricular fibrillation. If congestion occurs with little provocation, the future outlook is especially poor, although even here modern therapy may prolong life for a year or more.

When, however, pulmonary congestion is the result of mitral stenosis and not of left ventricular failure, and systemic venous stasis is due to chronic constrictive pericarditis or to a considerable degree of tricuspid stenosis or irreversible tricuspid dilatation, then life may last for many years, restricted to be sure, but often surprisingly comfortable.

It still remains the rule in congestive failure as otherwise, that "the larger the heart the worse the future," save for infrequent exceptions.

In closing I shall present a few pertinent remarks about treatment of congestive heart failure, the principles and details of which are so well covered in current textbooks and journals that they do not need repetition here. Digitalis, in any one of numerous effective forms, still remains the drug par excellence for myocardial failure, no matter what the heart rhythm, although the results are more spectacular in the presence of auricular fibrillation with rapid heart rate. We should, however, be quite sure that dyspnea or edema is of cardiac origin and not due to pulmonary disease or local stasis before we give it; this seems an obvious rule and yet I find it disregarded frequently, even in the best of clinics. Nor is digitalis of value when congestion is the result of chronic constrictive pericarditis unless auricular fibrillation has occurred as a complication to speed up the heart rate, in which circumstance it does help a lot. Also, it is of more than academic importance to avoid giving enough digitalis to upset the patient, inasmuch as the drug will probably be needed during the rest of the life of that individual and should not early be made excessively distasteful. Almost every instance that I have ever encountered of so-called sensitiveness or idiosyncrasy to digitalis is merely the result of physical or mental repugnance due to previous toxic dosage;

it is hard to combat this or to conceal the unpleasant taste although with persistence such difficulties can be overcome. I myself have never met an instance of true allergy to digitalis. There are three other observations about digitalis that I would add. The first concerns the occasional drug intoxication that immediately follows a vigorous diuresis by mercurial injection and which has been wrongly attributed at times to the diuretic; in such cases evidently a good deal of digitalis as well as water may be released quite suddenly from the tissues and hence it is well not to induce a very high saturation by digitalis. The second point concerns the different strengths of the digitalis preparations on the market in recent years. Many were increased in strength to accord with the international standard as recommended by the U. S. Pharmacopeia of 1936, the XIth Edition, while others have retained their old strength on which most of us have based our routine dosage for many years. Since the new potency is from 30 to 50 per cent stronger than the old, it behooves us always carefully to note the statements on the labels of the preparations we are using to avoid the possibility of disagreeable or even dangerous digitalis intoxication which I have found to have become, quite abruptly, increasingly frequent throughout the country in the last few years because of the general lack of appreciation of this important fact. The third point concerns the use of digitalis in modest dosage, say at the rate of one or one-half the usual daily ration without digitalization first, in cases of considerable myocardial strain and enlargement before the muscle fails, in order to prevent congestive failure. Dr. Henry Christian advised this some years ago and I believe that it is a wise move, despite the difficulty of proof of its efficacy.

I have but a word concerning the use of diuretics. Quite rightly the mercurials given intravenously have assumed an important and very useful role in the last decade or two, but there has arisen some neglect of the milder diuretics that may be taken by mouth and which may suffice as adjuvants to therapy by rest and digitalis.

Finally, I would urge the most careful attention to all the finer details of treatment—avoidance of nervous excitement and irritation, an atmosphere of quiet cheerfulness, a simple but adequate and tasty diet of small meals, limited salt and fluid intake and as few medicines as possible. Where life and comfort hang in the balance one cannot neglect a thing. Therefore, even though heart failure is the last stage of heart disease and, hence, not the most important, it is one of our impelling tasks, as physicians, to combat it as long as we can and to ease the sufferings of its victims.

ARTERIOSCLEROSIS: SOCIAL SIGNIFICANCE AND RECENT ADVANCES IN TREATMENT*

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A CONSIDERATION of the social significance of arteriosclerosis requires some definition of what is to be included under the omnibus term, arteriosclerosis. This common heading usually is applied to three different lesions. The first is atherosclerosis, the nodular type of vascular degeneration that affects chiefly the aorta and its branches but is also found in certain small arteries, particularly the coronaries and cerebral vessels. Although the exact cause of atheroma is unknown, it is generally conceded that it is a degenerative process of advancing years, which may or may not be associated with high blood pressure. The second type is the medial sclerosis of Mönckeberg. This form is seen particularly in the medium sized muscular arteries, particularly those of the extremities. Tortuous temporals and the pipestem radials are well known and common examples of this type of vascular disease. It bears no relation to high blood pressure, is found in older people and must be looked upon as a senile degenerative change. The third type is diffuse hyperplastic sclerosis which attacks the small arteries, is seen best in the arterioles of the kidneys and is intimately associated with hypertension. The condition has been well termed arteriolarsclerosis. It differs from the first and second types in that it is not primarily a degenerative change of old age. It is frequently encountered in younger people and is regarded by some as the reaction of the smaller arteries to the strain of prolonged high blood pressure.

With the exception of the last group, it is evident that the vascular lesions commonly referred to under the term arteriosclerosis, are intimately associated with the process of ageing and are encountered chiefly in individuals of the upper age groups. Although numerous examples of arteriolarsclerosis are observed in young people, the majority of individuals suffering from this form of vascular disease have attained to the

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later decades of life. It seems not unreasonable to suggest therefore, that there is a relationship between the vascular processes generally referred to as arteriosclerosis and growing old.

The present state of our knowledge makes it unjustifiable to state that age is the cause of arteriosclerosis or conversely, that arterial degeneration is the cause of old age. Winternitz and his associates are disinclined to regard arteriosclerosis as "primarily degenerative or the inevitable concomitant of age." There are others who disagree with this viewpoint. Alfred Cohn, for example, raises the query, "may not the inevitable concomitant of age be vascular change?" It is common experience to observe individuals who have attained far advanced years without exhibiting any evidences of arteriosclerosis. Conversely, many young people are encountered who have prominent signs of vascular degeneration. It may well be as William Boyd puts it: "The advance in years merely permits some slowly acting cause to produce the effect on the vessels." The oft quoted classic remark of Sir William Osler that "a man is as old as his arteries," still has much to commend it.

The relationship of arteriosclerosis to ageing involves the consideration of a problem that has long engaged the interest of outstanding philosophers and biologists. Is old age an involuntary phenomenon physiological in nature or is it disease? The most satisfactory discussion of this fundamental problem is to be found in the scholarly treatise on *Old Age* written some years ago by the late Aldred Scott Warthin. He pointed out that from embryonic life until death the processes of involution are constantly active and that the primary tissue changes observed in these involuntary processes are identical with those characteristic of ageing. Warthin groups the primary tissue changes of senescence under four heads: 1, numerical atrophy, the result of the gradual loss of power of cells to divide; 2, quantitative atrophy, the reduction in the size and number of parenchymatous cells; 3, shrinking and condensation of intercellular substance; 4, vascular changes, particularly vessel collapse and obliteration of lumen. These changes are inherent in the organism, inevitable and physiological, and, if undisturbed by environmental factors or disease, finally lead to failure of vital functions and biologic death. In the vast majority of individuals these primary involutionary processes are accelerated or modified by secondary pathologic changes of which those secondary to vascular lesions such as arteriosclerosis, with its attendant phenomena of thrombosis, embolism,

hemorrhage and atrophy, occupy a conspicuous place. It is these secondary pathological conditions that prevent most senile individuals from attaining their full life span. They embrace the causes of death which occur during the last third of life of which those due to degenerative vascular disease come first. A survey of the various causes of death at different ages for the general population of the United States emphasizes this. A little over 25 per cent of all deaths between the ages of 40 to 50 are due to cardiovascular conditions. The proportion of deaths due to this form of degenerative disease mounts steadily thereafter with each decade until between the ages of 80 to 89 it accounts for two-thirds of all deaths.

The adoption of such a conception of the mechanism of ageing is helpful in explaining the marked individual variations that are commonly observed in the rate of ageing and the symptoms of senility. Those in whom the intrinsic senile process progresses in an orderly fashion, uninfluenced by secondary pathologic changes and little affected by unfavorable environmental factors such as malnutrition, fatigue, trauma, infections and intoxications, may attain a ripe old age characterized by unusual mental and physical vigor. In this group are embraced the many outstanding examples of men and women who, in spite of extreme old age, have retained their creative ability and have accomplished some of the world's greatest works. On the other hand, there are those who, before they reach the age of 60, an age arbitrarily adopted by many gerontologists as the time at which old age begins, exhibit the physical and mental characteristics of advanced years. It is the secondary pathological changes rather than the essential age process itself that is responsible for the clinical manifestations of ageing in this group. It is Warthin's conviction that sclerosis of the arteries with its resultant effect upon the circulation and nutrition of organs becomes a chief collaborative factor in hastening or exaggerating the parenchymatous involutions of senescence, clinically recognized as premature age, and that the converse condition, deferred age, comes from the absence of any marked degree of arteriosclerosis. From the foregoing it seems not illogical to conclude that there is such an intimate association between arteriosclerosis and ageing that their social consequences are inseparable and for all practical purposes may be regarded as identical.

Acute disease, except when it occurs in epidemic form, has no broad social application. Its effect, regardless of how disastrous that may be, is

restricted largely to the individual and to those with whom that individual is in close social or economic contact. Such, however, is not the case when we consider a chronic disease of widespread and practically universal occurrence, of long duration, insidious and progressive in its course. Arteriosclerosis falls in this category.

The obvious social consequences of arteriosclerosis are those associated with the disabilities that occur as the result of its various serious sequelae, such as cerebral hemorrhage and thrombosis, myocardial failure, coronary occlusion, renal insufficiency and the different manifestations of cerebral degeneration grouped under senile dementia. In those in whom primary hypertension is the antecedent condition, some of these catastrophies may occur at a relatively early age, suddenly striking down individuals at the height of their productivity. For the most part the changes are insidious and their effects do not become apparent until the later years of life. In either event the social and economic results are the same. Those so afflicted, become incapacitated to a point where their earning power is lost or at least impaired. They become a burden upon their families and frequently, in the end, a charge upon the State. The amount of money involved in lost wages and the actual cost of their medical care and maintenance is difficult to estimate but it is plain that the annual cost runs into a huge figure which directly or indirectly must be borne by the wage earners of the nation.

The more remote and less apparent significance of arteriosclerosis presents much more important and far reaching consequences of social, economic, and political import. A proper understanding of these aspects of the subject demands some inquiring into the problems which have arisen as the result of the changing trend in the age composition of our population.

It is hardly likely that arteriosclerosis presented a serious social problem in the days of the Roman Republic when, it has been estimated, the mean length of life was between 20 and 30 years. The same was undoubtedly true in the early days of this country, for at the time when the Declaration of Independence was signed, life expectancy had reached only 35.5 years. By the turn of the century in this country, longevity had reached 50 years. From that time on life expectancy has steadily increased. By 1930 it was 60 years, at the present time 3 or 4 years have been added to this and it is estimated that within a few more decades it is reasonable to expect the span of life to have increased to 75 years.

It is interesting to note that this gain in life expectancy has occurred largely during the earlier years of life. By 1931, the expectation of life at birth in white males had risen to 58.84 years, whereas during the active years of middle adult life the increase in longevity has only been about one year. In the later decades of life, practically no gain has occurred. It is evident that this prolongation of life is limited largely to the younger age groups. As life expectancy has increased, the mortality in the first 10 years of life has notably decreased with no corresponding increase in mortality in the higher age brackets. These changes have resulted from improved control of the various infectious diseases, the virtual elimination of certain epidemic diseases, marked lessening of infant mortality, improved public health programs, a better understanding on the part of the people as a whole of the problems of diet, nutrition and personal hygiene, as well as a lessening of fatal accidents. Couple with this the fact that the birth rate of the United States is steadily declining, from 30 per thousand in 1900 to 16 per thousand today, it is easy to understand why the age composition of our population has undergone such a radical change which has brought about a startling increase in the number of older people. Further study of the age composition shows that whereas about one hundred years ago 52.5 per cent of the total population was under 20 years of age, today only 36.7 per cent fall into this group. Coincidentally the number of individuals aged 65 or over has increased. The middle of the last century they made up only 2.6 per cent of the total population, they now represent over 6 per cent and it has been conservatively estimated that in approximately another fifty years, more than 40 per cent of the entire population of this country will be 45 years of age or older.

With this amazing age increase comes a marked increase in the so-called degenerative diseases of which arteriosclerosis and its various sequelae occupy a commanding position. This is further emphasized by a study of the principal causes of death during the last 50 years which shows that the rate per hundred thousand of the various degenerative diseases has steadily risen whereas death from preventable diseases has undergone a conspicuous decline. Cardiovascular disease, which was fourth among the causes of death in 1900, now occupies first place. This is further borne out by the observations of Barker, who carried out complete clinical studies on a group of 300 new patients aged over 60 years. The diagnostic findings showed that cardiovascular disease was

by far the most common disorder in those between 60 and 70 years. The same was true in the older group of patients. As Christian has pointed out in a discussion of what he calls the non-preventable diseases, preventive medicine has saved life chiefly among the young thus enabling them to attain older years and to become the victims of degenerative conditions in the end. One significant result of the triumphs of medicine has been to bring about a material increase in the number of old people in our nation, thereby creating social and economic problems which cannot be ignored. In order to meet these increasing responsibilities adequately, it is essential that we show a greater interest in acquiring a better understanding of the psychological, social and economic needs of this increasing group of ageing arteriosclerotics in our midst.

Few people anticipate approaching old age with any degree of satisfaction. Many violently resent growing old and refuse to accept with equanimity their declining powers and increasing limitations. Examples of this mental attitude are the traditional disinclination of older women to admit their age and the resentment shown by so many patients when they are told that their symptoms are but the evidence of advancing years. This feeling of resentment against the inevitable, and this morbid dread of growing old is a source of much unhappiness and discontent among older people which is not infrequently reflected in unfortunate sociological consequences both in the home and in the community. It is not so much death that is feared by old people as the lurking dread of prolonged illness, a long period of idleness and even uselessness after a life of activity, and the loss of economic independence. It is the feeling of inadequacy, the thought that they are no longer essential and a lack of confidence in their ability to adjust themselves to changed conditions that are such disturbing factors to them. Continued advance in medical science will doubtless do much to lessen the suffering of the aged and to mitigate more and more, their physical handicaps. Improved medical care however, is not enough. It is the social aspects of the problem of growing old that must be solved. A means must be found to educate people to plan for their later years. Such a plan must involve more than an effort to accumulate enough money to sustain them in old age, although it is true that the assurance of economic security adds in no small degree to the peace of mind of those approaching senescence. This is well realized and has been given concrete expression in the social security and old age pension acts that have been instituted by the Fed-

eral government and many States. Although these pensions will to some extent meet the needs of the poor, they are obviously inadequate to allow most old people to live at the social and economic levels to which they have become accustomed and upon which their contentment depends to a considerable degree. There is a tendency to expect old people to accept compulsory retirement along with the dole. Such an attitude is both unfortunate and unsound sociologically and psychologically. The best insurance against unhappiness in old age is to be found in *occupation*. It is clearly the duty of society to educate older people to expect to make every effort to help themselves. The problem of providing useful occupation for this ever increasing group should be given careful study. They should not be asked to compete with youth or to labor with the same intensity that characterized their more active period of life. The present appalling situation with its wanton destruction of youth and the diversion of large numbers of young workers from productive occupations, furnishes illuminating examples of the effective ways in which the older element of a population, when necessity arises, can be occupied to advantage. E. V. Cowdry well sums up this aspect of growing old when he states, "The most effective preparation for advanced years is cultivation of some line of activity which can be carried on as we become more and more physically feeble. The really happy aged person holds his head high, consequently avoids a feeling of inadequacy because he or she is able to do something extremely well. It makes little difference what this something is as long as its value is apparent."

One of the most important problems connected with the social consequences of ageing, is the question of retirement. In an earlier generation when old people were much fewer in number, age was looked upon as a distinction. Today, in a social order which glorifies youth, it is held a liability. The current belief that after middle life enterprise, productivity, adaptability, and originality must decline has been widely accepted in both the professions and industry. The executive must leave the desk from which with wisdom and foresight he has directed a vast industry; the surgeon, at the height of his best clinical judgement, is forced to turn his back upon the hospital; the teacher, when his knowledge and intellectual powers have ripened into full fruition, finds the door of the classroom closed to him; all because society, still repeating the words of the Psalmist, "the days of our years are three score years and ten,"

written at a time when life expectancy was little more than 20 years, is convinced that at the arbitrary age of 65 the powers of all men must fail. There is no scientific evidence to show that there is any single age at which human beings of necessity experience significant loss of mental power. Activity of mind or body does not wear a man out except as it is influenced by environmental states such as accident, disease, malnutrition and discouragement. To be forced by retirement out of the active affairs of life, especially when one still retains a lively interest in and the ability to perform those accustomed duties, is one of the greatest shocks that can come to most individuals. When the stimulus of responsibility is withdrawn, the urge to effort ceases. Few individuals can successfully survive the inactivity of retirement. When the average man feels his usefulness is ended, the debilitating effects of old age come on apace. There are obvious reasons why it seems desirable to those who control our industries as well as our varied institutions to insist upon compulsory retirement at a given age. It affords opportunity for the advancement of younger men, makes room for the employment of others and introduces the vitality and fresh viewpoint of aggressive youth. It is unfortunate that retirement has to be placed upon such an arbitrary basis. It would probably serve the best interests of the individual, industry, and the community if some discrimination could be used so that those who, by reason of their experience possess exceptional judgement and administrative ability might be retained in some capacity of usefulness. The problem of the increasing millions of elderly persons who must and should have an opportunity to work is serious and calls for the wise and thoughtful consideration of our best minds.

Stieglitz has recently pointed out that industry is becoming acutely aware that the average age of their employees is increasing at a surprising rate and this in spite of the fact that a large number of unemployed existed until recently. The situation is becoming more acute as the present emergency creates a shortage in trained personnel and diverts many young men to the armed services of the country. It seems apparent that some means must be found by which older employees may be retained and productively employed in jobs suited to their capacity, so that their independence may be preserved and the value of their skill and experience not wholly lost to industry.

The question of increased retirement coupled with the steady rise in the age of our population is bringing about an economic and political

dilemma of far-reaching implications. It is a matter of record that during the last 75 years, the birth rate in this country has steadily fallen, there has been a relative decrease of children under 5 years of age and the relative number of persons over 65 has almost doubled. During this same period of time, the productive element of the population, aged between 20 and 44 years, has remained constant. Upon this latter group falls the chief burden of caring for the young and dependent older people. Child labor legislation, more time devoted to education and enforced earlier retirement of older workers is steadily diminishing the group of available productive workers, who find themselves confronted with the increasing responsibility of providing for the young on the one hand and an increasing number of non-producing older people on the other. It follows, therefore, that a dwindling group of producers is being called upon to provide for all the rest. In order to relieve the productive element of the population from this increasing burden, the government attempts to assume some of this responsibility. Such measures of social security, commendable as they may be, can only be provided for by increased taxation which in turn falls upon the industries and individuals that employ labor. In order to meet the needs of the non-producers, taxation is gradually being increased to the point where profits are eliminated thereby creating an unbalanced situation which involves conflict between the interests of producers and consumers.

This paradoxical situation has been graphically stated by Mark Sullivan who points out that although in the next 25 years the increase in the total population of the United States will be comparatively small, the increase in the number of old people will be rapid and great. Those aged over 65 will have increased approximately from 46,000,000 to 60,000,000; meanwhile, the number of productive workers aged between 20 and 65 will have remained about at their present level, around 80,000,000. This last class will be called upon to support, either privately or through taxation, a materially increased number of young non-productive individuals and a group of old people that will have doubled in number. The productive group of workers will be called upon to pay for the education of the young and pensions for the old. Although the total number of workers remains constant at about 80,000,000, it must be borne in mind that one-half of these are either unemployed or are housewives so that actually only about 40,000,000 producers will be called upon to support an equal number of their own age, plus the

increased number of young and old non-producers, a total which has been roughly estimated at 116,000,000. The political and economic potentialities of such a situation in which the burden of caring for the old and young will directly or indirectly be placed upon the productive workers of this country are far-reaching and to say the least, disquieting.

Aside from its economic aspects, there are definite political implications connected with this steady increase in the older element of the population, particularly if they are taught to expect early retirement and financial aid from the State. Such a group could readily become a pressure block of extreme political significance. If as a public policy we force this group of older individuals into idleness, we run a definite risk of placing American politics under the control of the senescent. Conservatism, caution and inflexibility are psychological characteristics of old age. The question has been raised whether democracy as we know it will continue to be as effective while our voting majority advances in age. Roy Helton has said that it will not be safe for America to permit the present psychology of old age to dominate even a powerful minority of our citizens. The situation has been aptly expressed by Professor John Dewey who writes: "Conservatism increases with age so that in the degree in which the older group expresses itself politically, we have the curious and indeed ironic condition that at just the time when measures of social readjustment are most needed, there is an increasing number of those whose habits of mind and action incline them to resist policies of social readjustment."

The increased incidence of degenerative diseases such as arteriosclerosis, due to the fact that more and more of the population are surviving to old age, is having and will continue to have a distinct influence upon medical practice. There is a growing demand upon physicians to meet adequately the medical needs of our ageing population. In order to do this successfully it is essential that we should acquire a better understanding of the altered physiology and psychology of old age, and the pathological processes peculiar to that period of life. Beginnings along these lines should be made in our medical schools where geriatrics should receive the emphasis that is warranted by its growing importance. As an ever increasing number of preventable diseases are brought under control, the non-preventable, degenerative conditions, notably diseases of the vascular system, are destined to make up the bulk of the physician's practice. Today this is already the case, at least,

in so far as concerns the internist.

In order to cope successfully with this changing trend in the practice of medicine, it is desirable that physicians should develop a more lively interest in and a better understanding of the problems of old age. Until recently, physicians, as a whole, have approached the degenerative diseases of later life in a defeatist attitude that has been as devoid of inspiration to the doctor as of comfort to the patient. Granted that diseases which are the result of degenerative change, such as arteriosclerosis are inevitable, and incurable, it is nevertheless incumbent upon the physician to approach their management in a spirit of greater cheerfulness and optimism. This is justified by the fact that if we will but make an earnest effort to acquire a better knowledge of the psychological and physiological needs of the aged, it is possible not only to prolong life but to relieve suffering, and restore to some degree physical and mental well-being that will do much to mitigate the handicaps and infirmities of age.

There is no condition characteristic of old age that is more deserving of our best therapeutic efforts than arteriosclerosis. Unhappily at the outset we find ourselves seriously handicapped in our efforts to treat this condition because of the lack of knowledge as to cause. The management of a disease of unknown or at best of suspected and multiple etiology, must of necessity be unsatisfactory. It must be conceded that the most effective approach to the control of any disease is its prevention. Of no disease is this more true than of arteriosclerosis. Thus far, unfortunately, in spite of much painstaking study, little has been accomplished along this line.

The most constructive progress that has recently been made looking to the prevention of arteriosclerosis is the work that has been done on what may be termed presclerotic conditions, of which none is more important than hypertension. Although hypertension and arteriosclerosis are in no sense synonymous, and hypertension cannot be said to be the cause of arteriosclerosis, it is undeniable that long continued elevation of blood pressure ultimately is associated with vascular changes due to the strain to which the arterial walls are subjected. This is particularly true in diffuse hyperplastic arteriolar disease. It is not surprising, therefore, that much effort has been directed to devising some method of reducing hypertension, particularly in that group of patients in whom the increased blood pressure is dependent presumably upon arteriolar

spasm and not secondary to chronic renal disease, hyperthyroidism, other endocrine disturbances or heart disease; a group, usually of younger age, suffering from the condition commonly referred to as essential hypertension.

It may be stated that the results of drug therapy in hypertension have been uniformly discouraging. Vasodilators, such as the nitrites, acetylcholine, sulphocyanate, aminophylline, have their place in the treatment of hypertensive paroxysms but are of no permanent value. The continuous use of small daily doses of suitable sedatives, which lower the patient's response to external stimuli, are of more value.

With the failure of medical measures to control hypertension, it is but natural that recourse should be had to surgery. On the assumption that the abnormal increase in blood pressure is the result of disturbances in the sympathetic nervous mechanism, operations have been devised which involve extensive sympathectomy. These include section of the anterior spinal nerve roots from about the 6th thoracic to the 2nd lumbar and section of the major and minor splanchnic nerves above and below the diaphragm. In some techniques partial removal of the adrenal glands has been combined with these procedures. These operative measures have been thoroughly discussed in the literature. From certain clinics have come encouraging reports indicating that in properly selected cases a definite reduction in blood pressure has been obtained which, in some instances, has persisted. The operation is a major surgical undertaking which involves prolonged hospital care and is not without definite risks. At present the results can hardly be said to be so consistently good as to justify its wide application.

A simpler and safer procedure is x-ray therapy, over the adrenals, the carotid sinus and the region of the pituitary. Such a plan has been followed recently by George Griffith of Philadelphia and his associates whose results are as yet unpublished. They have observed a permanent and satisfactory lowering of the blood pressure in an encouraging percentage of over one hundred patients with hypertension who were subjected to x-ray treatment. The plan consists of a series of six properly regulated x-ray exposures followed by an interval of from four to six weeks when it is repeated. Rarely more than two or three series of exposures are necessary to secure persistent and definite lowering of the blood pressure.

The most outstanding work on the etiology of hypertension and the

possibilities of its ultimate control has been that of Goldblatt and his associates who found that the production of renal ischemia, by clamping the renal artery in dogs and monkeys, could produce hypertension similar to that found in man, and that removal of the kidney the renal artery of which had been constricted, brought about a lowering of the blood pressure. It would be inappropriate to discuss this problem now when you are to be afforded an opportunity to hear Dr. Goldblatt on this subject. Suffice it to point out that his observations have focused the attention of urologists on the role that obstructive uropathies and other conditions that may interfere with renal circulation play at times in the production of hypertension. There are now numerous instances on record where removal of such obstruction has resulted in a prompt and permanent lowering of blood pressure. The possibility of such relief should not be overlooked in the study and management of patients who present prearteriosclerotic hypertension.

In any consideration of hypertension mention must be made of the highly suggestive work that is being carried on by Irvine H. Page, A. C. Corcoran and their associates. Their extensive experiments lead them to believe that renin, a protein formed in the kidney, and a renin-activator substance interact and form a third substance which they call "angiotonin." This latter substance is the true humeral vasoconstrictor capable of inducing increased arterial pressure in animals comparable to hypertension in man. They further have shown the existence in the body of substances which inhibit the action of these pressor substances. Other observers, Harrison, Grollman and Williams, have also demonstrated the presence of a humeral antipressor substance which they believe is elaborated by the kidneys. Although this work is still in a purely experimental state, clinical trials are now in progress on the effect of these antipressor substances on patients with hypertension. It would be premature to attempt to evaluate the practical results of these experimental observations, but it is not too much to hope that they will bring us at least nearer to the solution of the all important problem of the cause and control of hypertension.

A second prearteriosclerotic condition in the control of which marked strides have been made is diabetes. The relationship between diabetes and the premature development of arteriosclerosis of the atheromatous type is well-recognized and has been clearly discussed by Warren who points out that diabetics have not only more than their share

of arteriosclerosis but it falls to their lot 10 or 20 years earlier than in the non-diabetic. In the Philadelphia area during the year 1940, there were 913 deaths among diabetics. Of this number 337 died with, but not of, diabetes. This group included 146 in whom death was due to arteriosclerosis and its consequences. More prompt and effective treatment of diabetics, therefore, is another important step in the preventive treatment of arteriosclerosis. Closely allied to diabetes is the question of obesity, the proper control of which is also a valuable factor in the prophylaxis of arteriosclerosis.

Of all the suggested causes of arteriosclerosis there is none that is so well supported by innumerable careful observations and extensive clinical experience as heredity. When Sir William Osler made his oft quoted and somewhat facetious remark that the best way to prevent arteriosclerosis is to choose one's ancestors, he epitomized our knowledge of what is probably the most important factor in its prophylaxis. The hereditary control of such a widespread condition as arteriosclerosis obviously presents insurmountable difficulties. It leads us into the realm of genetics concerning which too little is known and understood by the physician. It is to be hoped that the future may bring to both the medical and the lay public a better appreciation of the far reaching significance of this subject. It is even conceivable that, as time goes on and the State assumes more and more regulation of our lives, some effort may be made toward the control of such conditions as arteriosclerosis by the enforced application of eugenic laws.

There is no subject that has evoked more discussion or that has given fadists greater opportunity than the role played by diet both in the development and control of arteriosclerosis. Much of the blame that has been placed upon diet as a cause of arteriosclerosis is unsupported by adequate scientific evidence. The widespread belief that diets high in protein and salt are responsible for vascular degeneration or for unfavorably influencing its course are ill-founded. It is true that when, as the result of arteriosclerosis, secondary changes are brought about in the heart or kidneys, so that failure of the former or insufficiency of the latter may supervene, a totally different problem is presented. Under such conditions, if the changes in blood chemistry warrant it, restrictions in the intake of proteins, salt and fluid are often necessary. With this phase of the subject at the moment we are not concerned. Attention is called to the fact that in certain types of arteriosclerosis, par-

ticularly those associated with hypertension, in which arteriolar spasm is alleged to be the underlying factor, salt free diets have been advocated by some observers who have claimed excellent results. The procedure is neither desirable nor applicable to arteriosclerosis as a whole. The unwarranted restriction of protein and sodium chloride over a long period of time has been productive of distinct harm to many, inasmuch as it has interfered with their electrolyte balance, impaired their nutrition and increased their anemia. There is more to be said in favor of restricting lipoids in the diet. Experimental evidence indicates that animals fed on diets high in cholesterol show lipid deposits in the aorta. In this connection, the work of Leary is most suggestive. By feeding rabbits with cholesterol over a long period of time he was able to reproduce with considerable fidelity, the lesions of human coronary atherosclerosis. The results are suggestive though the analogy may not be entirely exact in view of the fact that the metabolism of cholesterol in the rabbit is not identical with that in human beings. In countries in which, during periods of privation, the population had to subsist upon diets that were extremely low in lipoids, the incidence of atherosclerosis markedly diminished. On the other hand, Mallory calls attention to the fact that during the period when diabetes was treated by a high fat diet, there was an alarming increase in the atherosclerosis that accompanies that disease. Within the past 48 hours Professor Lester R. Dragstedt of the University of Chicago has presented experimental evidence to show that the pancreas secretes an hormone called "lipocaic" which enables the body to utilize fats, and that absence of this hormone plus a high fat diet produces experimental arteritis.

The effect of diet on longevity and the degenerative diseases of old age has been made the subject of a special study by Sherman. He holds that nutrition is a factor of equal if not of greater importance than heredity in the question of longevity. Sherman believes that if the known facts regarding proper diet are applied not only can the average life span be increased by 10 per cent but some of the degenerative forces within the body can be neutralized. He advocates an optimum diet, not merely an adequate diet and suggests that one-fifth of the food budget be spent for milk and cream, not less than one-fifth for fresh fruit and green vegetables and the remaining three-fifths for bread, butter, fish and eggs.

In the uncomplicated arteriosclerotic who shows no signs of cardiac

or renal failure, the effort should be made to retain a state of adequate nutrition, avoiding always over nutrition. Because of the tendency to anemia so prevalent in many older individuals, the use of liver twice a week as well as iron rich foods and iron, is frequently of advantage. It would be at variance with the spirit of the times to neglect to mention the role of vitamins in the arteriosclerotic's diet. Sherman is insistent that vitamins A and G are essential to the well-being of old people. The vitamins probably most needed and most useful are Vitamin B-complex and Vitamin C which may be given liberally. On theoretical grounds at least Vitamin D should be used with caution because it may prove harmful by increasing calcium deposits in the vascular tree.

Considerable diversity of opinion exists as to the role that infection plays in the production of arteriosclerosis. It is however, a sound therapeutic principle that whenever known foci of infections exist in the arteriosclerotic, they should be removed but in such a way as to induce the minimum amount of trauma and shock. There are those who lay great stress upon the importance of controlling that somewhat vague and ill-understood condition, intestinal toxemia, in the treatment of arteriosclerosis. It is difficult to appraise its significance until our knowledge of the subject is crystallized. It is obvious that adequate and regular elimination from the gastrointestinal tract is highly desirable. On the other hand, the practice of subjecting the arteriosclerotic subject periodically to the ordeal of violent purgation or, worse, to the much vaunted colonic irrigation is open to serious question. There is no adequate or unbiased evidence to indicate that either alcohol or tobacco are factors of etiological importance in arteriosclerosis. There is probably no harm in their continued moderate and proper use if the life habits of the individual are taken into account, and due consideration is given to the kind of a nervous system with which the patient is endowed.

The abortive and ironical efforts at rejuvenation which from time to time have had their enthusiastic advocates scarcely need serious consideration in a discussion of the treatment of arteriosclerosis. All the procedures thus far have failed—a result readily predictable if the pathology of old age is kept in mind. Furthermore, such suggestions are basically unsound, both from a biologic and physiologic standpoint, since they place undue emphasis upon the single factor of sexual activity. Other systems of the body, notably the cardiovascular and nervous sys-

tems are of far more importance in maintaining the health and well-being of ageing individuals. Until rejuvenescence of all the body tissues can be accomplished, attempts along this line are doomed to failure. With the rapid advances that have taken place in endocrinology, it is conceivable that ultimately some success in this direction may be obtained. To date the extravagant claims that have been made are based more upon fiction, than upon fact.

In conclusion, it is evident that although arteriosclerosis is one of the commonest conditions encountered by the physician, it is still one of the least understood. So long as its etiology remains shrouded in uncertainty its treatment will continue to be unsatisfactory. Meanwhile, as one of the outstanding causes of disability in old age, arteriosclerosis presents social, economic and political problems of national scope that dare not be ignored and which continue to challenge the scientific efforts and wisdom of the medical profession.

RECENT STUDIES IN THE PRODUCTION
OF CANCER BY CHEMICAL COMPOUNDS;
THE CONDITIONED DEFICIENCY
AS A MECHANISM*

The Bulkley Lecture

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ANY discussion of a topic as comprehensive as the chemical aspects of cancer must be limited, in order to avoid confusion, to relatively few phases of the subject. The two most important divisions are: first, the induction of cancer in man and animals by chemicals of known constitution; and second, the biochemical disturbances present in human beings afflicted with cancer of unknown etiology. To provide us with a better understanding of the way in which cancer is produced, it is desirable to correlate the findings in the organism in which we have caused cancer with the findings in the organism bearing a neoplasm of spontaneous origin. Perhaps in this way we can obtain an inkling of the etiology of cancer and very probably only through a knowledge of the etiology can we obtain information which will lead to prevention and cure.

It is desirable, then, at the outset to review briefly our knowledge of the chemical cause of malignant disease. This requires reference to Percival Pott,¹ the surgeon celebrated for his description of Pott's fracture. As you are probably well aware, he also described scrotal cancer in chimney sweeps as a disease of industrial origin, due to contact of chimney soot with the abraded skin of the worker. With the development of the coal tar and chemical industry in the middle and late eighteen hundreds, a mass of clinical information became available by which tar and tar products were established as causative of cancer in man. This clinical supposition was supported by experimental evidence when in 1912 Yamagiwa and Ichikawa² produced cancer of the rabbit's ear by the persistent application of gas-works tar. This classic experiment provided in an animal a suitable test object for the carcinogenic effect

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of chemicals, and led to the isolation from tar of pure compounds which were capable of inducing malignant disease (Cook and his co-workers³). As soon as these investigators had isolated one such substance, they immediately began to create, in the laboratory, many synthetic compounds structurally allied to it. This was done in an attempt to ascertain what peculiarity of chemical structure was responsible for the pathogenic effect. They found that, whereas no absolute rule could be laid down, most of the active substances produced were composed of benzene rings linked together, and whereas some modifications did not seem to impair activity, others, though very slight, removed completely the effectiveness.

While all this work was going on in other laboratories, an apparently unrelated but actually rather similar study was in progress. Many years ago Leo Loeb⁴ observed that the implantation of ovarian tissue into castrated male mice resulted in the production, not only of female breast structure, but also of cancer of the affected breasts. This observation suggested, of course, the hypothesis that some secretion of the ovary played a role in the production in mice of breast cancer. The correctness of this hypothesis was proved with the development, in the laboratories of sterol chemistry, of methods for the isolation of pure sex hormones. By these methods it was shown that the biological effect of the ovary is due to three chemically similar compounds: estrone, estriol, and estradiol.⁵ All three were found to be productive of breast cancer in mice, and the effect was in proportion to the relative abilities of the compounds to induce estrus. Moreover, at about the time that these studies were in progress, the establishment by the chemists of the structural formulae of the compounds made clear another significant fact. They resembled distantly in some respects the chemicals which Cook and his co-workers had derived from tar and found to be carcinogenic.

Here, again, the implication was clear. Certain compounds composed of multiple benzene rings, to which the body was exposed, either by external contact or from the processes of its own metabolic activity, possessed the power of causing cancer.

Another equally important fact became apparent from these studies. Not all mice possessed the same susceptibility to cancer produced by the administration of the pure carcinogenic compounds. Indeed, certain strains of mice are entirely immune to breast cancer which results from the administration of estrogenic substance.⁶ Furthermore, the strains which are susceptible are the strains which tend to develop breast cancer

spontaneously. The carcinogenic substances of the type derived from tar will induce cancer in almost all strains of mice, but careful breeding experiments show that here, again, there are distinct differences in the susceptibility.⁷

Not only do strain differences exist, but also different species of animals show marked variations in their tendency to develop cancer as a result of exposure to these compounds. Whereas mice are very likely to do so, guinea pigs are much less so, and rabbits almost not at all. In the primates, such as monkey or man, neither the synthesized tar constituents nor the sex hormones have been shown conclusively to have produced cancer. This extraordinary difference in susceptibility leads one to consider immediately the possibility that various species and various strains of the same species may differ in the manner in which they handle, destroy or detoxify those substances which have been shown to produce cancer. Obviously, if such a mechanism of detoxification could be shown to exist and the method by which it operates detected, it might be possible so to enhance detoxification that one could render immune an animal or a species ordinarily susceptible. Furthermore, if one could detect the mechanism of detoxification one could test various strains of animals, or indeed man himself, for the ability to effect this detoxification. Thus one would possess two powerful weapons: a method for the detection of the susceptible individual and a method for rendering him insusceptible. Such desirable objectives appeared to warrant a serious study of the manner in which animals dispose of and supposedly detoxify substances of a type which we know to be cancer-producing.

With this aim in view, some years ago at the Hospital of the Rockefeller Institute, Dobriner and I began studies of the manner in which rabbits, rats and mice handle administered carcinogenic substances. We had two very distinct leads. Cook and his associates⁸ had made the observation that none of their synthetic cancer-producing chemicals were active if a molecule of oxygen and one of hydrogen, grouped together as a hydroxyl group, were added to the original structure. Boyland,⁹ in England, had studied the manner in which animals handled dibenzanthracene, one of the compounds with which Cook had worked. He found that these animals excreted a phenolic, or hydroxylated, dibenzanthracene.

With these two observations at hand, our task was relatively simple. We only had to devise a suitably sensitive method for the detection of

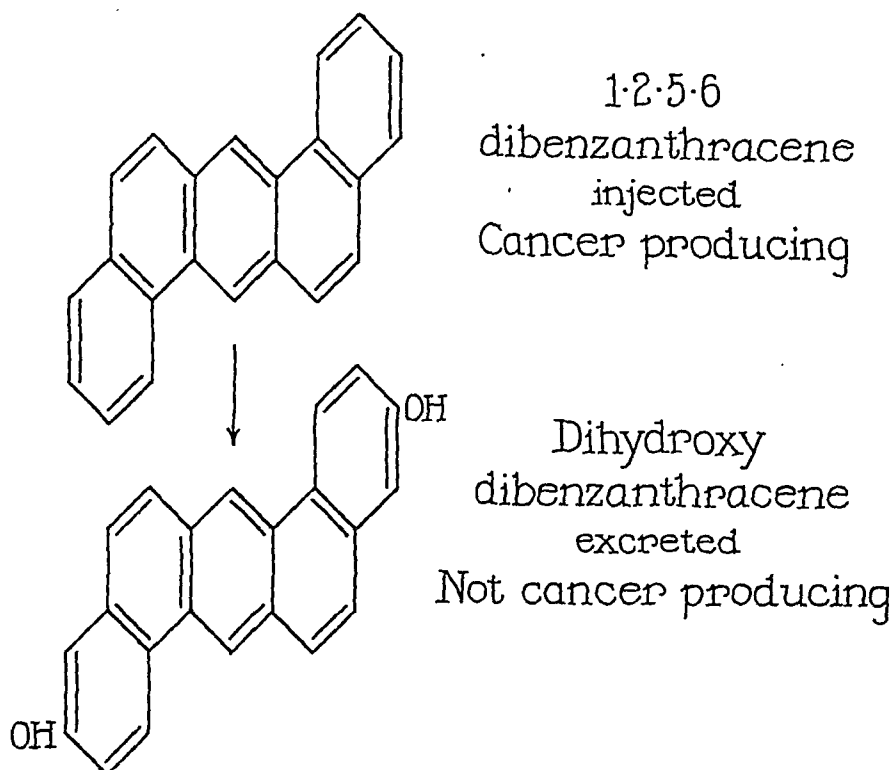


Fig. 1

dibenzanthracene and derivatives of it. With the aid of a grant from the Rockefeller Foundation, it was possible to apply the technique of absorption spectroscopy to this problem.¹⁰ You are probably aware that benzene-like hydrocarbons containing double bonds absorb certain wave lengths of ultraviolet light in a characteristic manner. By this characteristic absorption, it is possible to identify the compound causing it, even though the substance is present in exceedingly low concentration. Such an identification is more specific than any chemical method short of the actual isolation of the compound, and isolation is not possible when one deals with such very small amounts of material as those to which we were restricted. Once our method was perfected and applied, it was possible to show quickly and easily that if we injected dibenzanthracene into a rabbit, the animal excreted a small amount of the substance we injected as well as a large amount of some allied but quite different compound. This was equally true of the rat and the mouse. Furthermore, by chemical reactions we knew that the injected substance contained no hydroxyl group, whereas one or more were present in the material excreted. By the combination of chemical and spectroscopic methods, we

isolated the hydroxy dibenzanthracene into which the rabbit had converted the injected dibenzanthracene and acquired a sufficient amount of this new substance to test its power to produce cancer (Fig. 1). Through the courtesy of Clara Lynch of the Rockefeller Institute, we were provided with twenty-four mice of a strain highly susceptible to the carcinogenic effect of dibenzanthracene. Twelve animals were injected each with 4 mg. of that compound in oil, and twelve littermates of these animals each with 4 mg. of the dihydroxydibenzanthracene. All of the mice which received dibenzanthracene developed tumors at the site of injection, while none of those which received the dihydroxy compound did so. It seemed clear that the rabbit, at least, converted dibenzanthracene into a non-carcinogenic hydroxy derivative, and hence the conversion could be considered to be a protective one. Only recently a confirmatory study has been published by Boyland.¹¹ Once the fact of a protective conversion was established, it became important to ascertain upon what factors it might depend.

We speculated a great deal concerning what role in the conversion might be played by vitamins because we knew that many of the important chemical processes of the body were carried out by enzymes or ferments of which vitamins form essential parts. Furthermore, we suspected that the conversion of dibenzanthracene took place in the liver and we were aware that the liver is rich in vitamins because it is there that the enzyme systems for which vitamins are essential are particularly active and numerous. We immediately attempted to ascertain whether a deficiency of vitamins played any role in the ability of the animal to detoxify dibenzanthracene. Unfortunately, trouble was immediately encountered because our methods, while qualitatively excellent, were quantitatively insufficiently accurate to provide us with unequivocal information.

By sheer good fortune, however, just at that time an ideal experiment came to hand through the work of the Japanese group headed by Kinoshita.¹² This investigator had observed that a dye, butter yellow, composed of two benzene rings linked together, regularly caused liver cancer in rats fed a diet composed of unpolished rice and carrot. If liver or yeast was added to this regime, no cancer occurred. Here, clearly, was an experiment in which a dietary constituent rich in its content of the vitamins of the B complex was protective against induced cancer. To what was this effect due? An elaborate series of experiments has been

carried out, and it will not be profitable here to discuss all of them in detail.¹³ Certain facts were made clear, however. In the unpolished rice and carrot diet fed by Kinoshita, at least two factors are lacking. One of these is a pure vitamin, riboflavin, and the other is a so far unidentified constituent of casein.¹⁴ When these two substances are fed as a supplement to the rice diet, distinct, though incomplete, protection is provided. It is clear, then, that for the first time it has been shown that a deficiency of dietary constituents can render animals susceptible to one type of cancer and that supplement with those constituents protects them almost completely.

To ascertain what factor or factors were lacking in the diet of unpolished rice, it was necessary to establish, if possible, the existence of any deficiency in the bodies of the animals susceptible because of the diet. Since the liver is the principal site of action of those chemical systems called enzymes which depend for their activity upon the presence of vitamins in their molecules, it was reasonable to examine the content of vitamins in the livers of the susceptible rats. This was done by Kensler and his co-workers¹⁵ in my laboratory.

A chemical method was available for the measurement of one important vitamin, riboflavin, but no procedure for the estimation of the activities of the enzyme systems in which it functions was at hand. A very small amount of riboflavin was found in the livers of the rats fed the rice diet which rendered them susceptible to liver cancer from butter yellow. Furthermore, the content of riboflavin in the rice was less than is supposed to be the minimum amount required to keep rats in good health. Moreover, the amount of riboflavin excreted by the rats taking the rice diet for a considerable period was very much lower than the amount excreted by normal rats. When the carcinogen, butter yellow, was added to the diets, the animals eating it apparently spilled in the urine their reserve riboflavin. Lastly, as previously stated, the addition of riboflavin with casein to the deficient diet afforded definite, though incomplete, protection against the cancer. In short, from the evidence presented the fact was clear that riboflavin participated in some way in the protective effect provided by dietary supplements, and that its lack played some role in inducing susceptibility to cancer production by butter yellow.

The importance of riboflavin in the etiological mechanism suggested immediately that the vitamin interacted in some way with the chemical

which caused the cancer and perhaps had to do with its detoxification. The validity of this suggestion still remains to be established, although it is still under investigation in my laboratory. The possibility itself, however, warranted a study of the activity, in the livers of the various groups of animals, of the kinetic enzyme systems of which vitamins form essential parts.

As stated before, no method was available for the measurement of any riboflavin enzyme. Dexter, in my laboratory, had developed, however, an excellent and relatively simple procedure for the measurement of the activity of Coenzyme I or diphosphopyridine nucleotide. That enzyme system is concerned with fermentation and depends upon the vitamin nicotinic acid as an essential constituent. Kensler¹⁵ applied this method to the study of the livers of the experimental animals. The results provided particularly significant information. In the rats fed only the diet which makes them susceptible to cancer from butter yellow, the livers showed no decrease in the content of Coenzyme I. If butter yellow was added to the diet, however, a prompt and serious decrease in the amount of the coenzyme occurred. This drop developed long before the malignant new growth was apparent and could not be correlated with simple destruction of liver tissue. The Coenzyme I content of the tumor was even lower than the content of the substance in the adjacent non-malignant liver tissue. On the other hand, if the deficient diet and butter yellow were fed with some protective supplement, such as yeast, perfectly normal liver levels of Coenzyme I were found, and, of course, no cancer occurred.

The observation just described was of considerable fundamental importance. It proved, for one thing, that a liver cell cancer could grow widely and rapidly, apparently well-nourished, even though its content of an essential vitamin, riboflavin, was much lower than was found in normal liver tissue. More striking still, the observations proved that the administration of the cancer-producing chemical interfered in some way with the activity of an enzyme system, Coenzyme I, of which another essential vitamin, nicotinic acid, is a part without which the enzyme will not operate. We were certain that the diets contained adequate amounts of the vitamin and, furthermore, the rat has been shown not to require dietary nicotinic acid to maintain health. Nevertheless, the vitamin in the tissues of the animals used in these experiments was certainly made non-functional if butter yellow was fed. In other words, butter yellow

blocked the activity of nicotinic acid in the livers of the experimental rats. Hence, no matter how much free nicotinic acid was available, the livers were in a state of nicotinic acid deficiency as serious as that found in the livers of dogs with black tongue, the analogue of pellagra in man.

It appeared, then, that a "conditioned deficiency" clearly had been established; a vitamin deficiency due, not to failure of the animal to ingest the vitamin, but to some interference with the function of the vitamin in the form in which it is biologically active. The existence of such a "conditioned deficiency" had been postulated previously, but it had not been proved to exist. What implication, then, has the fact that a pure chemical, in this instance the carcinogen butter yellow, had been shown to cause disease, in this instance cancer, by blocking the functional activity of a vitamin, in this instance nicotinic acid? The principle of the "conditioned deficiency" so demonstrated might be applicable to any number of disease processes hitherto poorly understood.

Further proof of the thesis of the "conditioned deficiency" was required. It was obtained as follows: Clearly, the oral administration of carcinogenic butter yellow produced a serious loss of Coenzyme I (the enzyme which contained nicotinic acid) activity in the livers of the treated animals. Hence, an *in vitro* test should be possible, as follows: Butter yellow, or some metabolic product of it, should decrease the rate of respiration of the surviving liver slice, a rate dependent in part upon the function of Coenzyme I. More specifically, and more conclusively, the carcinogen or its metabolites should block, in the test tube, the function of the nicotinic acid-dependent Coenzyme I.

To make the experiment required the isolation and identification of the breakdown products of butter yellow excreted by animals fed that compound. This was done in my laboratory by Dobriner and Stevenson.¹⁶ The chemical steps involved, as discovered by these investigators, are presented schematically in Fig. 2. Amido-phenol and paraphenylene diamine, both free and both acetylated, were isolated from the urine of rats fed butter yellow. These, with the carcinogen originally administered, gave five compounds to test *in vitro* for their effects on the pure Coenzyme I system. These tests were made and very interesting results obtained. Only one of the metabolic products, paraphenylene diamine, inhibited the activity of the enzyme system. The other four were almost wholly inactive.

This observation suggested immediately the trial of dimethyl para-

Butter Yellow

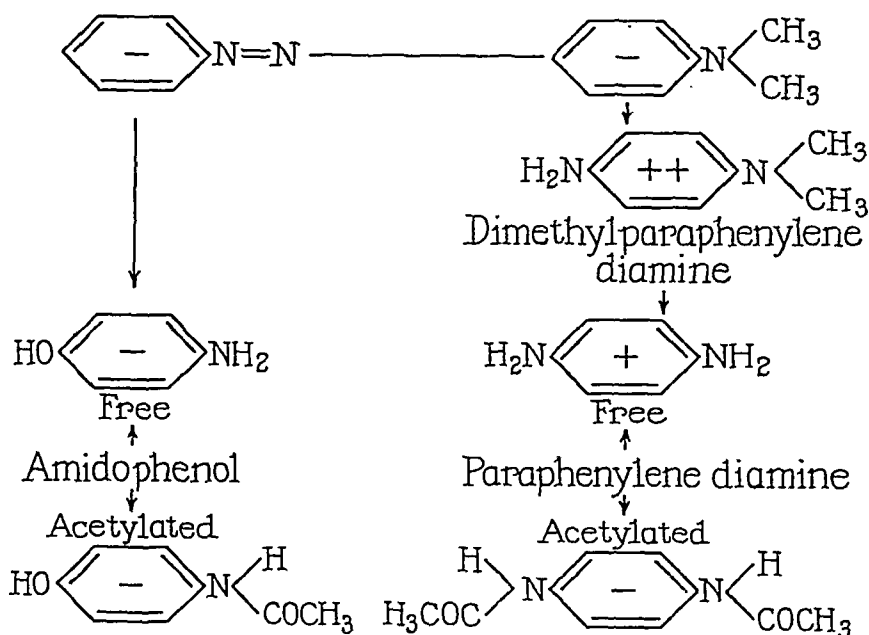


Fig. 2

phenylene diamine which, though not isolated, probably is the precursor in the liver of the paraphenylenediamine formed by the metabolic breakdown of butter yellow in the body. The dimethyl compound was tested and was found to be even more toxic to the Coenzyme I than was the simpler compound into which it is converted. The results of these experiments on the toxicity of the various butter yellow metabolites are presented in Table I.¹⁷ It should be noted that the conversion by the body of the paraphenylenediamine as well as of the dimethyl compound to acetyl derivatives is a detoxification mechanism, since the acetylated substances are completely without toxic effect on the enzyme system studied.

From the experiments just described, then, evidence was provided to substantiate our original assumption. *That is, that the administration of at least one carcinogenic chemical injured normal cells by interfering in some way with an enzyme system which is essential for their normal chemical function and so their normal life.* The results suggested, furthermore, that this principle of the poisoning by a specific chemical of at least one, and possibly more than one, normal enzyme system caused

TABLE I
Effect of Acetylation on Toxicity

| System | mm. CO ₂ in 1st hour |
|---|------------------------------------|
| Control | 488 |
| Control and dimethylparaphenylenediamine | 78 |
| Control and acetyldimethylparaphenylenediamine | 520 |
| Control and paraphenylenediamine | 95 |
| Control and mono-acetylphenylenediamine | 488 |
| Control and diacetylphenylenediamine | 498 |
| Concentration of compounds = 1×10^{-3} molar | |

the normal cell to become a cancer cell. An analogy can be drawn, perhaps, to the polycythemia which occurs in human beings as an adjustment to the anoxemia of great altitudes. Even more pertinent, possibly, is the analogy to the mutations which result from the persistent exposure of tissues to such physical agents as x-ray.

If these analogies hold; that is, if some permanent alteration of liver cells is caused by the prolonged poisoning of a normally required enzyme system, and if this alteration is characteristic of the cancer cell, another experiment should be possible. The fact should be demonstrable that the liver cancer cell, produced by the administration of butter yellow and the persistent breakdown of that substance to its derivative dimethyl paraphenylene diamine in the liver, is capable of respiring normally in the presence of a concentration of the dimethyl compound which poisons the respiration of normal cells. This experiment has been done, and the results establish the validity of our assumption. The respiration of a normal liver tissue suspension is inhibited by a concentration of dimethyl paraphenylene diamine which appears to be without effect on the respiration of a suspension of cancer tissue which developed supposedly as the result of the intoxication of normal liver tissue by the same compound. This difference does not hold for liver slice, however, and we have no explanation at present for this fact. In short, the enzymes of the cancer cell can operate in the presence of a compound

which, in the same concentration, is poisonous to the enzymes of the normal cell.

It appears probable, then, that as far as liver cancer is concerned, the malignant cell differs radically, as concerns the chemical systems which make its life possible, from the normal cell from which it is derived. It appears likely, furthermore, that this chemical difference is due to the change required to enable the cell to survive in spite of a chemically induced "conditioned deficiency" disease.

I am sure that the question will be asked immediately, "What bearing have the results of this set of experiments on the cause and cure of cancer in man?" It is not possible to answer this question at the present time. This much may be said, however. The studies suggest the necessity of a careful and precise examination of a large number of patients bearing malignant neoplasms in order to ascertain whether or not they show any evidence of an interference with chemical systems of which vitamins form essential components. Even more important, however, would be studies based upon the evidence presented that at least one type of malignant cell, that of butter yellow liver cancer in the rat, is immune to the chemical which probably causes it to develop.

If evidence of a "conditioned deficiency" in man were obtained, and if we knew exactly upon what alterations it depended, the correction of the disorder, and so the prevention of cancer, might be conceivable. If the second suggestion is confirmed and other types of malignant cells proved to differ from the normal cells of their origin in respect to their resistance to pure chemicals, the road to chemotherapy might be opened.

Both of these hypotheses are wholly speculative at present, and further study may well prove both to be untenable. Until such evidence is at hand, however, it is at least of some interest, and may be of some importance, to speculate about the "conditioned deficiency" and the induction of malignant neoplasms.

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THE HISTORY OF FEVER THERAPY IN THE TREATMENT OF DISEASE*

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THE idea that fever is a method of therapy may be traced back to the early days of written history. "Give me the power to produce fever, and I will cure all disease," is a quotation attributed to Hippocrates more than twenty-three hundred years ago. Ruphos of Ephesus, four hundred and fifty years afterwards, said: "If indeed any were so good a physician as to be able to produce fever, it would not be necessary to look for any other remedy in sickness."

The production of fever as a therapeutic procedure had to wait centuries, however, for advances in chemistry, physics, mathematics, and medical sciences. The development of fever therapy can be divided into empirical and scientific eras. The borderline between these two eras was thermometry which was introduced in the early part of the Seventeenth Century by Galileo and Sanctorius, and developed in the second half of the Nineteenth Century by Wunderlich and Allbutt.

EMPIRICAL ERA

The origin of therapeutic fever lies buried in medical antiquity. While the rays of the sun have therapeutic value, other than their heating effects, nevertheless, early physicians used them solely for these effects. Heat was also applied to locally affected parts of the body and to its entirety by means of hot water, steam, sand, and mud baths. It is probably true that the ancient therapist might not have been aware of the fact that by these physical means he produced a rise in body temperature. However, our present knowledge of thermotherapy leads us to the reasonable conclusion, based upon the descriptions of the techniques used, that sufficient heating energy was frequently employed to accomplish such an elevation of systemic temperature.

Egyptian physicians during the Fifth Century B. C. applied rules for

* Read May 14, 1941, at the joint meeting of the Section of Historical and Cultural Medicine of The New York Academy of Medicine, and the New York Physical Therapy Society.

sun and heat therapy. In the encyclopedic compilations of Oribasius (325-403 A. D.) of Constantinople, are found quotations from Herodotus, the historian of the Fifth Century B. C., referring to this phase of Egyptian medicine.

Natural hot air caverns connected with volcanic sources were utilized (Oribasius, X, 40). The epic poet Homer (Fifth Century B. C.) clearly established that hot baths for medical purposes were common among the Greeks before the Age of Pericles.

Hippocrates had ideas as to the significance of fever, and modern concepts as to its possibilities. He prescribed hot water and steam baths for "thickened" and "tense" skin, for "spasticity" and for pains of the extremities as well as of the torso. Illustrative is the case history of a man of Athens who was affected with a severe pruritus of his entire body. The skin in all regions was so thickened that he had the appearance of a leper and it was impossible to pinch up the skin anywhere. No one had been able to relieve him. Hippocrates ordered him to go to the Island of Melos where there were hot baths. There he became entirely cured of his itching and the thickening of the skin, but he developed a dropsy and died. This man may have had one of the chronic dermatoses for the treatment of which dermatologists are now finding fever therapy to be of value. It is also possible that this patient may have received burns sufficiently extensive to cause a nephritis which proved fatal.

Among contraindications, Hippocrates mentioned repeated or profuse nasal hemorrhage, which, as an evidence of hypertension, would be included in modern contraindications for fever therapy.

During the reign of Tiberius Caesar, 42 B. C.-37 A. D., Aurelius Cornelius Celsus described the prevailing medical procedures and ideas regarding fever and heat. He wrote of a certain Pretonius who treated persons attacked by fever somewhat as follows: "He had the patient well covered up to excite at the same time a violent heat and thirst. When the fever began to abate somewhat, he made him drink cold water. If he broke out in a violent sweat, the patient was considered cured." "Heat," Celsus wrote, "acts well in eye diseases which are without pain and lachrymation. It is good for all sorts of ulcers but principally those due to cold." The techniques of heat application included wet fomentations, dry packs, steam baths, hot air baths, and sun baths. Celsus claimed that ordinarily heat would "relax the skin and draw forth corrupt humors, and change the condition of the body."

Galen wrote: "It is probable that Erasistratus (an Alexandrian anatomist of the Fourth Century B. C.) was not unaware of the method of treating cases of dropsy by heating in the barrel, a treatment which is highly estimated by other ancient physicians. Indeed, the patients experienced for the entire body an evacuation (sweating) much greater and sooner than in the bath. However, they did not suffer from the heat because they breathed cold air, their heads being outside. If they are deprived of this air, they die quickly." (*Deutil respir.* 4. t. iv.)

Coelius Aurelianus treated wasting, hemoptysis, and dropsy with dry hot air and hot sand baths. A description of the early hot sand bath is found in the works of Oribasius (*Orib.* Col. X, 8). "The summer time is the best because one can then choose the hottest day. Toward morning, there are prepared on the river bank in the deep sand, two or three trenches. These are allowed to become thoroughly heated by the sun. The patient should have digested his last meal and also taken a previous walk or at least had some passive movement. When the air is sufficiently warm and the sand sufficiently heated the patient is laid in the trench and covered with the hot sand as much as he can comfortably bear. The head must be protected from the sun. His face is wiped with a sponge dipped in cold water and if he suffers much he is given something with which to rinse his mouth. If the patient perceives that his body does not heat up at all or that he even becomes chilly because of the sweating he should say so. The attendant will then remove the sand, take him out of the trench, and will place him in the trench alongside in the same way as described above. If necessary, this may be done a third time being guided by the different conditions and according to their strengths."

The American Indians treated fevers with heat. William Penn in a letter to Edward Baynard, a fellow of the Royal College of Physicians, described how an Indian Chief obtained almost immediate relief from an illness associated with fever by the use of hot vapor baths. Among the early Americans, the sweat bath was a favorite therapeutic measure, especially for acute fevers. Arthritis, neuritis, and rheumatism, common among these Indians, were not distinguished from each other, but were all treated alike with the sweat bath. Carolina Indians used hot mud holes for treating various diseases of the extremities. Remittent and other forms of fever prevalent among the inhabitants of Northern Africa, were treated by sweating induced by hot sand and hot water baths.

The Chinese and the Japanese were among the earliest peoples to use their intensely hot springs for therapeutic purposes. In Japan the volcanic formations gave rise to many hot springs. These thermal springs were used for the treatment of all forms of syphilis, arthritis, rheumatism, acute genito-urinary infections, and respiratory, digestive, nervous and ocular diseases. They have been very popular throughout the Japanese empire since the Sixteenth Century and enjoyed local renown for several centuries before that time. Indeed, the use of the thousands of hot springs in Japan was common among all classes of the populace as one of the most important cures long before the introduction of European medicine. At Kusatsu, water gushes out of the bases of ancient volcanoes at a temperature between 100° F. and 160° F. As the water flows into reservoirs, it is unbearably hot, and the bathers stir it with large wooden paddles, thereby cooling it. They then immerse themselves to the neck and pour hot water over their heads with wooden dippers. After three to six minutes of this refined torture, they bob out almost parboiled with a body temperature of between 103° and 105° F.

SCIENTIFIC ERA

The research techniques developed during the Seventeenth, Eighteenth, and Nineteenth Centuries, permitted medical practice to pass from the stage of philosophic argument to scientific reasoning. Galileo in 1595 invented the thermometer, which may be said to have brought science to fever and heat therapy. Galileo's thermometer was the open-air alcohol thermoscope. Shortly afterward, in 1611, Sanctorius introduced this device to clinical medicine. Sanctorius investigated the cause and nature of body temperature. To carry out his studies, he devised the pulsilogium, an instrument for studying the pulse, and applied Galileo's thermoscope. He recognized that the human body has a normal temperature and determined variations from the normal as an aid to diagnosis.

In 1648, Von Helmuth also began to use a clinical thermometer, designed by Leurchon, the Frenchman, who in 1624 gave the name "thermometer" to the instrument.

Ferdinand II, Grand Duke of Tuscany, hermetically sealed the open end of Galileo's thermometer in 1641. Robert Hooke of England, in 1664, proposed that the freezing point of water be taken as one fixed point on the thermometer scale. It is believed that in 1684 he also sug-

gested the boiling point of water as another fixed point.

Fahrenheit described the use of mercury in thermometers in 1714. Herman Boerhaave (1668-1738) of Leyden, the founder of "eclectic" medicine, had been interested in fever and temperature reactions. He directed Fahrenheit to make him some thermometers for clinical use.

In 1742, Celsius of Upsala, an astronomer, proposed "zero" as the boiling point of water and "100" as the temperature of melting ice. The change to modern Centigrade was made independently by two scientists, Christin of Lyons, and Stromer, a colleague of Celsius. Stromer inverted his friend's scale and this revised instrument was used experimentally at Upsala in 1750.

Some of the authors of the Sixteenth and Seventeenth Centuries regarded fever as nature's means of healing. Gomez Pereira and Solenander pointed out the common belief of the Italians that tertiana had a cleansing effect. Primrose quoted the belief of people in England that malaria was beneficial.

An engraving by Jacques Lainet (Paris, 1659) represented the combination of mercury and heat for the treatment of syphilis. Fumigations with mercury were carried out in an oven. The intense sweating along with salivation, was thought to rid the body of disease poisons. "For one pleasure, a thousand pains" was the significant inscription on the oven.

In attempts to discover the exact influence of heat, Boerhaave and his pupil, Prevoost, and Fahrenheit put animals into heated ovens. They found that a dog and a cat died in twenty-eight minutes at a temperature equivalent to 73° C., while a sparrow died in seven minutes.

Influenced by Sydenham's views and by his own observations, Boerhaave finally concluded that fever must not be fought under any circumstances. He wished, he said, that he could produce the febrile curing action by artificial means. "I would be," he said, "the greatest physician if I could produce intermittent fever as easily as suppress it."

John Hunter (1728-1793), the English surgeon, also used the thermometer. Both he and DeHaan opposed the view that the production of heat in the body was due to friction of blood moving in the vessels. George Martine, of Scotland, in 1740 published his clinical-thermometric observations in a paper called "Essays and Observations."

Boerhaave's praise of fever caused a controversy that has persisted up to the present time. Gaub. one of Boerhaave's pupils, believed that

although fever was often salutary, nevertheless, it sometimes was fraught with great danger, especially to the circulation.

In 1790, Metzler made an interesting observation on malarial therapy in a treatise, "On the Advantages of Fever in Long Standing Diseases." This treatise, published in Ulm, was one of the early prophesies of the future therapeutic use of malaria. Metzler wrote: "Vigorot, Broussonet and myself sent patients with congested bowels to such places where they have soon been cured by intermittent salutarious fever."

An important theory on the cause of fever was offered by William Cullen of Edinburgh, in 1777. It was based on the newly acquired facts in the budding field of neuropathology. Virchow one hundred years later was a protagonist of this theory. An elevated temperature of the body, Cullen said, was a paralytic symptom due to depression of a natural influence on heat production. Any disease could become febrile if it extended to the centers of metabolism and suppressed the moderating effect of these centers. Febrile patients were, therefore, subjected to cooling measures by Cullen and his followers.

With rare exceptions, no attempt was made prior to the work of Wunderlich, to obtain more than one or two temperature recordings during an illness. Davy (1788-1829) in mapping out physiologic variations, and Traube (1818-1876), closely following the influence of digitalis on the body's temperature, were among the few who made frequent observations during a twenty-four hour period. The importance of such continued readings escaped them. Traube denied that fever depended upon increased production of heat. Lavoisier's theory of combustion and oxidation had postulated this relationship.

Up to the time of J. Clasius (1850) heat was generally regarded as a material substance. Only after Lord Kelvin (Sir Thomson) in 1849 established his absolute scale of temperature and Clasius and Helmholtz in 1850 worked out the mathematical laws governing heat transformation was the scientific framework for clinical thermometry laid.

In 1868, Carl Wunderlich published his classic on animal heat. Wunderlich demonstrated the diagnostic and prognostic importance of continued temperature observations during the course of a disease. He recorded the temperature of patients every four hours and constructed charts showing its variations. When he stated that fever was a symptom and not a disease, Wunderlich prepared the way for studies on heat production and fever. Wunderlich's method of attaining rectal tempera-

ture curves characteristic of various diseases spread quickly through England and Germany.

The period of the Nineteenth Century that witnessed the introduction of thermometry into clinical medicine was characterized also by advances in knowledge concerning infectious diseases. The record of the temperature of the body became one of the principal means of characterizing various febrile affections and of recognizing complications of these diseases. The close association of infection with fever was soon established and stressed so energetically that at present physicians find it difficult to avoid using one as an indication of the other. Thermometers had begun to make their appearance in numerous English hospitals during 1866-1867, and became generally accepted within the next two years. These were axillary thermometers, large, ten inches long, clumsy, and took five minutes to register. Sir Clifford Allbutt in 1868 reduced their size and devised the clinical mercury thermometer with which we are familiar. Resistance thermometers and thermocouples now permit of the continuous observation and automatic recording of temperature. Thanks to these advances, the thermometer, well-established as the invaluable tool of the diagnostician, has become the compass of the fever therapist.

The practitioners of the ancient and of the medieval world had made therapeutic use of fever produced by physical means on an empiric basis. They did not realize the physiologic significance of the procedure. The voices of those who reacclaimed the value of systemic temperature elevation and stated that fever is a natural mechanism of defense were drowned out under a deluge of antipyretics. Cool packs, showers, and baths, snow and ice were applied with such diligence that at times the doctor in concentrating on his efforts to reduce the fever forgot the patient, and accidents occurred. Less dangerous and simpler antipyretic measures were sought. Sydenham had called attention to the value of quinine in treating the fever of malaria. It came to be generally used for the treatment of other diseases associated with temperature elevation, such as typhus, puerperal infections, and tuberculosis. In these cases quinine proved unsatisfactory. A search for new antipyretics was therefore begun. Salicylic acid, phenol, antipyrin, antifebrin, amidopyrin, followed one another and were prescribed alone, alternately, or together. Chemists, in their laboratory search for antipyretics, discovered many a useful narcotic, analgesic and spasmolytic drug, but the "fever

drug" could not be found.

When Pfluger (1829-1910), as a result of his physiologic studies, ascribed a utilitarian purpose to fever, he was studiously ignored. Welch's supposition, in 1888, that "fever-producing agents light the fire which consumes them" found no response until recent years. Virchow echoed Cullen. Practitioners maintained a continuous attack on temperature elevation in disease. The momentum of these opinions has carried over into our day, so that the alcohol sponge and cold baths still are frequently routine, and the combination of acetylsalicylic acid, phenacetin and caffein has remained a popular method of "reducing the fever."

A clearer and more scientific conception of fever and its beneficial effects was obtained through several revolutionary medical discoveries which resulted in the founding of bacteriology and in an understanding of human metabolism, nutrition, and the physiology of the nervous system. The bacteriologist has shown that, in order to overcome disease, the objective of the clinician should not be the direct suppression of the abnormal elevation of temperature, but rather the destruction of the foreign agents responsible for inflammation and for fever. Further investigations demonstrated that the value of quinine in the treatment of malaria was not due to the influence of this drug upon heat production, heat loss, and heat regulation, but because of its effect upon the plasmodium. The work of men such as Pasteur, Koch, and Behring helped to establish the idea that the body fights for itself, that suffering life helps itself and the art of the doctor should assist the natural power of healing when it is weakened or limited. Modern medicine should no longer concentrate its attention upon the number of degrees of temperature elevation, but upon the profound change in physiologic activity due to this elevation. It should determine to what extent these phenomena are symptoms of the healthy activity of the organism and to what extent they are signs of damage and of loss. We recognize that microorganisms are not the only cause of inflammation and of fever, but that there are a host of thermic, chemical and toxic causes.

As early as 1870 Wunderlich declared that fever is a neuropathologic process. Other outstanding scientists of that time, such as the physiologist Johann von Muller, the surgeon Billroth, and the pathologist, Virchow, agreed that fever is an increase of oxidative processes due to stimulation of the central and peripheral nervous system. Experi-

mental hyperthermia was produced by the famous brain puncture (Warmestich) of Aronsohn and Sachs (1884), who stimulated the corpus striatum, and by Ott (1891), who stimulated the tuber cinereum. The studies of Krehl and his associates further emphasized the neural relationship to fever. The work of Krehl confirms more and more the famous conception of Liebermeister, who had declared that in fever, heat regulation is adjusted to a higher level.

Space does not permit reference to the work of many men who helped develop these fields. These include Lavoisier (1775) who determined the fundamental fact that the quantity of oxygen absorbed and carbon dioxide excreted depends upon food, work, and temperature; Joule, who in 1842 determined the mechanical equivalents of heat; Mayer, Helmholtz, Bischoof, Voit, Rubner, Atwater, Benedict, Lusk, Bazett and many others.

In 1883, W. H. Phillips experimenting upon himself, demonstrated that his temperature could be raised to 103° F. by prolonged immersion in hot water. Fourteen years later, Hill reported the influence of bath temperature upon body temperature and the changes it produced in pulse, blood pressure, and alveolar tension. Others confirmed and added to these findings. These authors included Fox, Sonntag, Weichbrodt and Jahnel, Schamberg, Tseng, Walinski and Mehrstens and Pouppirt.

Kellogg, in 1894, reported that the body temperature, as indicated in the rectum, may rise to 103° F., or even higher, in a prolonged electric light bath. Yet no one thought of using his technique for producing artificial fever for therapeutic effects until 1929, when Kahler and Knollmayer obtained fever temperature by this means.

With the advent of modern electricity, it was soon recognized that one of the effects of an electrical current was thermal. However, no form of electrothermal treatment had been possible until d'Arsonval in 1891 evolved his high frequency current, and showed that it would pass through the human body in a volume as great as three amperes, but without muscular nervous irritation and causing what he called "an unpleasant sensation of heat."

Nikola Tesla, working independently, produced a high frequency circuit and reported his results in the same year as d'Arsonval. He noted the passage of this current through the body and its lack of effects other than heating, which he suggested might be used therapeutically. It remained for von Zeynek, nearly ten years later (1904), working with

von Preyss and von Berndt, to demonstrate the therapeutic application of this current. von Zeynek called the method thermopenetration, while Nagelschmidt finally hit upon the now accepted term *diathermy*.

Notwithstanding the voluminous literature upon diathermy accumulated all over the world, it was not until 1929, nearly forty years after d'Arsonval's discovery, that a sustained fever induced by diathermy was used for therapeutic purposes. Neymann and Osborne, King and Cooke, raised the body temperature by using jacket-shaped electrodes. By means of blankets, they were able to maintain such temperature elevations for several hours.

The recent interest in fever therapy was in a large measure the result of work by Wagner-Jauregg of Vienna and by Whitney of Schenectady. Julius Wagner-Jauregg, after twenty years of observation, began to inoculate parietic soldiers with malaria in 1917. Despite some fatalities and great resistance from his colleagues, his success was so brilliant that ten years later he received the Nobel prize. The beneficial effect of malaria in epilepsy had been known to Hippocrates. Its curative effects in paresis and in insanity had been recorded in more than one hundred and sixty cases before Wagner-Jauregg, according to Maisani. Yet Wagner-Jauregg's work popularized this procedure and established its clinical value so that it received world-wide study.

In order to achieve the same results a host of less noxious proteins than the living malaria plasmodium were tried. Physical agents, such as the hot bath, diathermy, and phototherapy were also employed.

In January 1928, Whitney observed that the men working with high-powered short wave tubes employed for long range radio transmission complained of headaches and other discomforts. A physician examining these men before and after work found that exposure to the current developed by these tubes produced two or three degrees of temperature elevation. Although Gosset and his co-workers had treated tumors on geranium plants by means of short waves in 1924, and Schereschewsky had employed currents of very short wave length for the treatment of animal tumors, these workers did not call special attention to the heat-producing effect of these energies. After experimentation on small animals, Whitney placed a number of larger high-frequency oscillators at the disposal of a number of us who were especially interested in the subject. From these and other sources have come new data concerning the physiologic significance of fever and also its thera-

peutic possibilities in the treatment of gonorrhea in all of its manifestations (including cases resistant to the sulfonamides), syphilis of the central nervous system, Sydenham's chorea, rheumatic fever, and in some diseases of the eye and of the skin. A voluminous literature on the subject has been developed consisting of books and articles which have been printed in leading medical journals. At the First International Congress on Fever Therapy held in New York in 1937 much of the data developed in recent years was summarized. There is evidence of the possibility of enhancing the effectiveness of the newer chemical substances by combining their use with purposeful elevations of the body temperature as in syphilis, gonorrhea, and in subacute bacterial endocarditis.

This survey of fever research gives but a bare outline of the painstaking work devoted to this subject in the past years. We tend to view fever therapy as a modern concept because the techniques which we employ to create it are of recent origin. It is therefore of interest to note that this method has been employed by some physicians all through the period of known medical history. Many of the diseases which we treat in this manner today were apparently treated in like fashion during the past centuries. It may well be that we still have something to learn from the ancients, including Petronius who thought that fever should be treated with heat.

In spite of all these efforts of the past, the significance of fever is not sufficiently appreciated today. It is hoped that the precise production of hyperthermia and its control in time and degree by means of the new methods will prove not only a most useful contribution to therapy, but will also start a new chapter in the history of the time-honored problem of fever.

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PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

NOVEMBER 6—*The New York Academy of Medicine*. Executive Session—a] Reading of the minutes; b] Amendment to By-Laws; c] Report of Nominating Committee. ¶ Papers of the evening. Aviation Medicine—a] The relation of the medical and physical sciences in the development of aviation, Detley W. Bronk, Ph.D., Sc.D., Professor of Biophysics and Director of the Johnson Research Foundation, University of Pennsylvania School of Medicine; b] The use of oxygen in aviation medicine, John R. Poppen, Captain, Medical Corps, U.S.N., Bureau of Aeronautics, Washington; c] Bends and the effects of acceleration, John F. Fulton, Sterling Professor of Physiology, Yale University School of Medicine. ¶ Report on election of Fellows.

NOVEMBER 27—*The Harvey Society in affiliation with The New York Academy of Medicine*. The second Harvey lecture, "Factors Conditioning Resistance to Epidemic Influenza," Thomas Francis, Jr., Professor of Epidemiology, School of Public Health, University of Michigan.

SECTION MEETINGS

NOVEMBER 5—*Dermatology and Syphilology*. Presentation of cases—The Mount Sinai Hospital. ¶ General discussion. ¶ Executive session.

NOVEMBER 7—*Surgery*. Reading of the minutes. ¶ Presentation of cases—a] 1. A case of congenital overgrowth of a finger to huge proportions, with post-operative result, 2. A case of mucocele of the appendix with pseudomyxoma of the peritoneum, Francis X. Timoney; b] A case of primary pneumococcus peritonitis in an adult treated by ex-

ploration, sulfathiazole and specific serum, with recovery, Robert A. Wise. ¶ Papers of the evening—a] Thoracoscopy and pneumonolysis. Observations on 100 consecutive cases, Louis Carp, Borris A. Kornblith; b] Surgical problems of the present war, Fraser G. Gurd, McGill University (by invitation). ¶ General discussion. ¶ Executive session.

NOVEMBER 11—*Combined Meeting of the Section of Neurology and Psychiatry and the New York Neurological Society*. Reading of the minutes. ¶ Case presentation—Choreo-athetosis and athetosis, a clinico-pathological report, M. Neustaetter; Discussion, Tracy J. Putnam. ¶ Papers of the evening—a] Mimetic smiledness as related to handedness: an indicator of basic modes of human adaptation, John G. Lynn (by invitation); Discussion, Charles Davison; b] Marginal dyskinesias and dyssynergias as diagnostic adjuncts (Moving pictures), Byron Stookey, Lester Mount (by invitation); Discussion, Israel S. Wechsler.

NOVEMBER 12—*Combined Meeting of the Section of Historical and Cultural Medicine and the New York Society for Medical History*. Reading of the minutes. ¶ A symposium on approaches to medical history, Richard Harrison Shryock (by invitation), Iago Galdston, George Rosen (by invitation), Fritz Wittels. ¶ General discussion.

NOVEMBER 12—*Pediatrics*. Round table discussion—School Health Regulations, Philip M. Stimson, Chairman. From the view point—a] Of the public school, Isidore H. Goldberger; b] Of the private school principal, Millicent C. McIntosh (by invitation); c] Of the private school physician, Katherine Dodge; d] Of the parents, Virginia Fox Patterson (by invitation); e] Of the Bureau of Preventable Diseases, Department of

Health, Samuel Frant (by invitation); f] Of the Department of Health, Haven Emerson. ¶ Executive session.

sion, Benjamin S. Barringer, Henry G. Bugbee, Thomas J. Kirwin. ¶ General discussion. ¶ Executive session.

NOVEMBER 17—*Ophthalmology*. Executive session—Reading of the minutes. ¶ In memoriam—Francis Wayles Shine, Bernard Samuels. ¶ Presentation of cases— a] Tuberculous sclerosis in a five-months-old infant, Isadore Givner; Discussion, F. L. P. Koch (by invitation); b] Actinomycosis of the conjunctiva, associated with superficial punctate keratitis, Gordon Bruce; Discussion, James K. Duryea; c] Lymphosarcoma of the lacrimal gland, Charles A. Perera; Discussion, Maynard C. Wheeler. ¶ Papers of the evening—a] Vollmer Patch Test; its possibilities in ophthalmic practice, Benjamin Friedman and Frank Keil, Jr. (by invitation); b] Current studies on the mechanism of formation of the intraocular fluids, Jonas S. Friedenwald, Baltimore (by invitation); Discussion to be opened by Ludwig V. Sallmann (by invitation).

NOVEMBER 18—*Medicine*. Reading of the minutes. ¶ Papers of the evening—a] Bone marrow—diagnostic and therapeutic considerations, Maurice Morrison (by invitation); b] Treatment of leukemia by radioactive phosphorus, Lloyd F. Craver; c] Hematologic complications following chemotherapy, Nathan Rosenthal; d] The differential diagnosis of the hemolytic anemias, Thomas Hale Ham, Thorndike Memorial Laboratory (by invitation); Discussion, William Dock (by invitation), Paul Reznikoff. ¶ Executive session.

NOVEMBER 18 — *Genito-Urinary Surgery*. Reading of the minutes. ¶ Papers of the evening—a] Manipulative treatment of ureteral calculi, William Niles Wishard, Jr., Indianapolis (by invitation); b] Carcinoma of the ureter—report of five cases, Albert Bothe, Philadelphia (by invitation); c] Modification of the Higgins technique of uretero-intestinal anastomosis, Joseph A. Hyams; Discus-

NOVEMBER 19—*Otolaryngology*. Executive session—Reading of the minutes. ¶ Papers of the evening—a] Effect of tonsillectomy on respiratory infections in children, Albert D. Kaiser, Rochester, New York (by invitation); b] Relationship of tonsil and sinus infections to chronic arthritis, Ralph H. Boots; c] Effect of tonsillectomy on nephritis, John Lyttle; Discussion, Westley M. Hunt, Robert L. McCollom (by invitation). ¶ General discussion.

NOVEMBER 21—*Orthopedic Surgery in conjunction with the Philadelphia Orthopaedic Club*. Reading of the minutes. ¶ Papers of the afternoon (*Discussion by invited speakers*)—a] Congenital absence of tibia, lower half, bilateral, aged 15 years. Result of observation and treatment since early infancy, Arthur Krida; Discussion, J. T. Rugh; b] Femoral ischial transplant, David M. Bosworth; Discussion, Bruce Gill; c] Angioma of tarsal bones, Samuel Kleinberg; Discussion, George Wagoner; d] Suspensory ligament operation for pathological dislocation of the hip following poliomyelitis, Joseph B. L'Episcopo; Discussion, B. F. Buzby; e] Eosinophilic granuloma of bone, Henry L. Jaffe; Discussion, Irvin Stein; f] The laminagraph as an aid in the treatment of chronic osteomyelitis, Alan DeForest Smith and Lawson E. Miller; g] Observations in the topical use of sulfone derivatives, Major Edgar M. Bick; Discussion, A. R. Shands, Jr.; h] A case of Guillan-Barré disease, H. Leslie Wenger; Discussion, A. M. Rechtman; i] Stenosing tenovaginitis of the thumb in infants, Isidore Zadek; Discussion, Rutherford L. John; j] Arthroplasty of the first metacarpal greater multangular joint for dysfunction following a mal-united Bennett's fracture, Nicholas S. Ransohoff; Discussion, Ernest Brav; k] A modified operation for opponens

paralysis, T. Campbell Thompson; Discussion, J. T. Nicholson. ¶ Executive session—Special election, John C. McCauley, Jr., for Secretary.

NOVEMBER 25—*Obstetrics and Gynecology.* (Program presented by the Obstetrical Department of the Morrisania Hospital.) Executive session—Reading of the minutes. ¶ Presentation of cases—a] Macrocytic anemia of pregnancy, Mark Daniel (by invitation); Discussion, Bernard S. Kahn (by invitation); b] Unilateral cortical abscesses of kidney, complicating pregnancy, Frederick A. Wurzbach, Jr.; Discussion, Thomas M. Mulcahy (by invitation); c] Blood transfusion reaction due to atypical agglutinins, Philip Crooks (by invitation); Discussion, A. S. Weiner (by invitation) and Philip Levine. ¶ Papers of the evening—a] Management of unengaged vertex presentations in primiparae, Abraham B. Tamis and Jacob Clahr; Discussion, Milton J. Goodfriend; b] Contractions of the human uterus in pregnancy and labor, Leo Wilson. ¶ General discussion.

AFFILIATED SOCIETIES

OCTOBER 30—*New York Pathological Society* (in affiliation with *The New York Academy of Medicine*). Paper of the evening—The pathology of diabetes mellitus, Shields Warren, Boston (by invitation);

Discussion by Arthur C. Allen (by invitation, Irving Graef. ¶ Executive session.

New York Roentgen Society—Because of conflict in dates with the Graduate Fortnight, this Society held no meeting in October.

NOVEMBER 17—*New York Roentgen Society* in affiliation with *The New York Academy of Medicine*. Papers of the evening—a] The roentgen features of carcinoma of the lung in relation to operability, I. Sarot (by invitation); b] The preoperative localization of lung abscess, C. B. Rabin (by invitation); c] Sectional radiography in the recognition of suppurative lung disease, Marcy L. Sussman. ¶ Discussion, H. Neuhof (by invitation), H. Wessler (by invitation). ¶ Executive session.

NOVEMBER 27—*New York Pathological Society* in affiliation with *The New York Academy of Medicine*. Presentation of cases—a] Uterine tumor of endometrial stroma type, Amour F. Liber, Chester R. Brown; b] Myoblastoma of voluntary muscle with lipid-containing cells, Chester R. Brown, Amour F. Liber. ¶ Papers of the evening—a] Infection with organisms of the Salmonella group, Siegbert Bornstein (by invitation); b] Lymphosarcoma with special reference to the original site, Nicholas M. Alter. ¶ Executive session.

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BULLETIN OF
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FEBRUARY 1942

INFLUENCE OF EXTRINSIC FACTORS ON
THE CORONARY FLOW AND CLINICAL
COURSE OF HEART DISEASE *

N. C. GILBERT

Professor of Medicine, Northwestern University Medical School

THERE are a great many clinical observations associated with heart disease, and especially with angina pectoris, which are difficult to explain only on the basis of intrinsic anatomical changes in the coronary vessels alone, and can best be explained by the assumption of vasomotor changes in the caliber of the coronary vessels, decreasing the flow volume. Such an assumption of vasomotor changes is not new, and has been made by a great many men at many times. I would like here to review some of the experimental and clinical evidence indicating that such a decrease in flow may occur in response to autonomic stimuli of various origins, and that such decreases in coronary flow from extrinsic factors may produce the same disproportion between blood supply and blood needs, as do intrinsic anatomical changes in the vessel walls, which restrict the coronary flow when additional demands are made upon it.

I am not unmindful of the importance of the intrinsic factors. The point which I wish to make is this, that both intrinsic and extrinsic factors are valent in the restriction of coronary flow in proportions which

* Presented October 22, 1941 at the Graduate Fortnight of The New York Academy of Medicine.

vary in different cases. But the intrinsic factors are not reversible, and the conditions imposed are permanent, and must be compensated for in various ways by various means. The extrinsic factors are reversible and their influence may be lessened or may be obviated altogether.

It is not necessary to enter into a discussion of the nervous control of the coronary vessels. I think that it may be assumed as rather generally accepted that the vagus nerve exerts a tonic vasoconstrictor effect upon the coronary vessels, varying in degree with different physiological conditions, and that vasoconstrictor impulses are carried by the vagus. In like manner, it may be assumed that vasodilator impulses are carried through the sympathetic fibers, and that there is also some degree of vasodilator tone present in the vessels.

Anrep,¹ in 1926, described a reflex vasoconstriction of the coronary arteries consequent upon increased intracephalic pressure. The pathway for this vasoconstrictor impulse was through the vagus. Stella² and others confirmed this, and showed that this was mediated through the carotid sinus.

Clinically, attacks of angina pectoris or of paroxysmal dyspnea are seen to occur occasionally when the blood pressure reaches a point higher than that usual for the individual. That the attacks are not always due to an increase of the heart's work with the increased pressure, would seem to be indicated in the cases reported by Lewis,³ in which the pain came on at a certain high level of blood pressure, and was relieved by the coronary vasodilator action of nitroglycerin, even though there was no fall in pressure.

The increased tendency to anginal pain following meals is a frequent clinical phenomenon. The symptoms may be explained in part by the increased work demanded of the heart during the earlier periods of digestion. This does not explain, however, why the pain is so frequently relieved by belching gas, or why it occurs at one time and not at another in the same person, under the same conditions. Anginal pain is very frequent also in hiatus hernia. The pain is more apt to occur when the herniation is present and is less apt to occur when the hernia is reduced.

That the anginal pain in these cases is due to a reflex vasoconstriction of the coronary arteries, is shown by the work of Dietrich and Schweigl in 1931, working with von Bergmann.⁴ Distention of the stomach in the dog caused a marked decrease in the coronary flow, and this was espe-

cially so if the distention was at the esophageal hiatus. This decrease in flow did not occur after atropine, or if the vagi were sectioned. Fenn, LeRoy and I⁵ repeated this work, with similar results. We further confirmed these results in the unanesthetized dog by distention of the stomach before and after atropine after a Rein stromuhr had been previously placed upon a branch of the coronary artery. Also, if the free abdominal cavity were distended with air, we again obtained a decrease in coronary flow, but not after vagotomy or atropine.

We obtained clinical confirmation of these experiments, using the method of Levy,⁶ in which anginous patients are asked to breathe a low oxygen mixture until the first symptoms of anginal pain appear, when the patient is switched to straight oxygen and the attack ceases at once. If the patient breathed this low oxygen mixture after a meal, the pain came on sooner than it did in the control experiments done upon an empty stomach. If atropine was administered before the meal, the pain on a full stomach came on no sooner than it had originally in the control experiments. However, there were two groups of these patients in whom the time appearance of the pain was deferred by atropine. In some of them, the pain after a meal and after atropine came on at the same time as it had in the control experiments. In some others it took a longer time for the pain to occur after atropine than in the control, even though the experiment was done upon a full stomach. This would seem to indicate that in this second group, in which the pain did not occur as soon as in the control, the pain was due not only to intrinsic changes in the vessel walls, but to an extrinsic increase in vagal tone which had been released by the atropine. We then did another series of experiments upon the same patients, with an empty stomach, exactly as in the control experiments, but here we administered atropine before the experiment. In these experiments, the patients fell into the same two groups. One group experienced pain after the same time interval as in the control experiments, without the atropine. This group was the one in which there was more clinical reason to assume intrinsic changes in the vessel walls. The other group did not experience any symptoms for a longer time than had been noted in the control experiments, and a still longer time than that noted in the experiments done after a full meal. This group was that in which there was more clinical reason to assume the presence of an increased vagal tone, in addition to intrinsic vascular changes.

There is no need to emphasize the clinical importance of these observations in view of the frequency of anginal pain after meals. Master⁷ has also shown the greater incidence of coronary thrombosis after meals.

In the experiments upon dogs, it was noted that the decrease in coronary flow was more marked if the distention was at the cardiac end of the stomach, and especially if the distending bag were against or in the esophageal hiatus. While hiatus hernia is being diagnosed more frequently than before, there is reason to think that it is still underdiagnosed, and its importance not fully realized. In a series of one hundred and seven cases of anginal pain followed in the last two years, in forty-four patients examined roentgenologically, there were eighteen or 17 per cent who showed a hiatus hernia. Just what the figure would be for a control series, I do not know, as I know of no control series to which some objection could not be made. But I do know that in the series of patients with angina pectoris and hiatus hernia, under our observation, there was a very clear history indicating the influence of the herniation upon the occurrence of the anginal pain, and that medical management of the hernia was apparently a factor in relief of these patients. It is to be emphasized that the anginal pain in hiatus hernia is not merely "anginalike," but that it is a real anginal pain resulting from an insufficient blood supply to the heart muscle.

Dr. Van Dellen has a case of hiatus hernia under observation at present, in which the electrocardiogram is normal when the herniation is not present, but in which there is a typical coronary curve present when the hernia occurs.

Hiatus hernia may also induce attacks of paroxysmal auricular fibrillation. I have seen two such cases in the last two months, in which there was very clear evidence that the attacks came on with the incidence of the hernia, and disappeared when the stomach slipped back into place. There is every reason to think that this occurrence is mediated through the vagus.

von Bergmann showed also that coronary vasoconstriction resulted from stimuli having their origin in the esophagus. We have all of us seen patients in whom attacks of angina were precipitated by the act of swallowing. Anginal pain is also found associated with diverticula of the esophagus and diverticula at the cardiac end of the stomach. Weiss and Ferris⁸ reported a case in which Stokes-Adams attacks were brought

on by the act of swallowing. They showed that it was a vago-vagal reflex, and that it was clinically relieved by atropine.

Attacks of angina pectoris associated with gall bladder disease have been reported by several authors. Schwartz and Herman⁹ reported that in most cases of gall bladder disturbance associated with cardiac symptoms, the heart symptoms were less after the operation. Fitz-Hugh and Wolferth¹⁰ also showed an amelioration of the cardiac symptoms after gall bladder surgery, and showed that electrocardiographic changes tended to return to normal.

Some experiments which Fenn, LeRoy and I did upon the anesthetized dog could be interpreted as showing that there was a decrease in coronary flow upon distention of the gall bladder, but we did not consider our results wholly conclusive. In the last few weeks, Sheridan and I have repeated these experiments upon the decerebrate dog, and have obtained definite evidence of a decrease in coronary flow upon distention of the gall bladder, or distention or irritation of its ducts. This reflex did not occur after vagotomy, or after atropine.

It is possible, also that stimuli resulting from other abdominal conditions may initiate vasoconstrictor effects upon the coronary arteries. Angina pectoris is frequently associated with duodenal ulcer, a spastic duodenal bulb, a spastic colon, or diverticulosis of the colon. One can not be certain, however, how much the anginal symptoms are a result of reflexes arising from the abdominal conditions, and to what extent the anginal pain results from a common tendency to respond more readily than normal to vagal influence, or to the same lack in both cases of some inhibitions of this reflex, from higher centers. Experimentally, Smith and Miller¹¹ have shown that vagal reflexes may originate in the colon, as well as in the gall bladder. The part played by the gastrointestinal tract in producing cardiac symptoms has recently been reviewed by Morrison and Swalm.¹²

Danielopolu¹³ long ago considered that stimuli arising from intrathoracic conditions might institute reflexes which decreased coronary flow, and such a thesis was in part the basis for operative interference to interrupt that reflex.

Scherf and Schönbrunner¹⁴ in 1937, published observations showing that lung emboli were associated with anginal pain, and similar observations have been reported since. DeTakats, Beck and Fenn¹⁵ presented evidence indicating that there was a coronary vasoconstriction asso-

ciated with the lodging of an embolus in the pulmonary vessels, and that this was a reflex mediated through the vagus. The cases of heart block associated with pulmonary emboli reported by Kauffmann¹⁶ would indicate vagal stimulation by the embolus. DeTakats and his co-workers have also shown a constriction of the pulmonary vessels, and of the bronchi, associated with pulmonary embolism.

DeTakats and Jesser¹⁷ consider that such coronary vasoconstriction is the cause of death in many cases of pulmonary embolism, and that death is not always due to asphyxiation or right heart failure or incomplete venous return to the heart. Acting upon this hypothesis, and treating cases with atropine and papaverine, or atropine and aminophylline intravenously, resulted in a decrease in the death rate in their cases of pulmonary embolism from 82 per cent to 13 per cent.

Even more important from a clinical standpoint, is the work of Manning, McEachern and Hall,¹⁸ showing that when a coronary artery of the dog is ligated, there is a reflex vasoconstriction of the other coronary vessels. When a coronary artery of the dog was ligated under full anesthesia, there was a very low mortality. But if the ligature were placed about the vessels under full anesthesia and not tied until several hours later, after recovery from the anesthetic, there was a very high mortality. But if the vagi were cut or atropine administered before the artery was ligated in the unanesthetized dog, the mortality remained at the same low level as when the artery was tied in a dog in which the reflexes were abolished by full anesthesia. In some work that has not as yet been published, LeRoy, Gilbert and Fenn have shown that when the artery is ligated, the mortality is not only less with atropine, but even less if a purine-base vasodilator is used.

These observations of Manning, McEachern and Hall are of very great clinical importance in the management of coronary thrombosis. Making use of these observations, we have very greatly reduced our mortality in early cases of coronary thrombosis, by the immediate administration of atropine and aminophylline. In addition, it must follow that if this secondary vasoconstriction was obviated, the infarct would be smaller and the myocardial damage less, with a better recovery and less loss of function. Recovery has been more rapid and more uneventful in our cases, than previously.

What we have said so far has concerned only reflexes mediated through the vagus. There are also reflexes mediated through the sym-

pathetic, which are constantly active, and tend to increase the coronary flow in response to increased needs. Failure of this normal vasodilator mechanism of the sympathetic, or an inhibition of the sympathetic, would necessarily result in an inability of the heart to adapt itself to its changing needs.

It has been known for a great many years that the pulse rate could be slowed by stimulation of the nasal mucous membrane in animals, and that this effect could still be obtained by the same stimulation after vagotomy or atropine, or both. The blood pressure might rise, or might remain unchanged. This can only be explained by assuming an inhibition of sympathetic tone.

These observations would seem to afford a possible explanation of the attacks of angina pectoris which occur when an anginous subject suddenly breathes cold air through the nose. Such attacks may even be fatal.

In order to determine if there might be a loss of sympathetic vasodilator tone in the coronary arteries, associated with what appears to be a sympathetic inhibition, experiments were done upon the decerebrate dog, in which the coronary flow was measured.¹⁹ Upon stimulation of the nasal mucous membrane with cold water, or chloroform vapor, a decrease in coronary flow was observed, associated with a slowing of the pulse, and a rise in blood pressure. After vagotomy, or atropine, the same event occurred.

If ergotamine tartrate was administered to dogs in doses corresponding to those used clinically, for its sympathetic inhibitor effect, the same sequence of events occurred as was seen upon stimulation of the nasal mucous membrane. Vagotomy or atropine did not abolish this effect.

When experiments were done upon anginous subjects, inducing anginal pain by means of breathing a mixture low in oxygen, the pain was found to appear much sooner if ergotamine were administered before starting the experiment.

The experiments with ergotamine tartrate upon the dog, and upon the anginous subject are open to the objection that in each case the ergotamine tartrate may have exerted a direct vasoconstrictor action upon the coronary vessel walls. Katz²⁰ has shown such an effect in the empty beating heart of the dog and we have confirmed it. But I am not at all certain that these observations altogether settle the question of a direct action upon the vessel, and I would feel that much further work

is necessary. The curves representing the effects of stimulation of the nasal mucosa, where there is no question of any drug acting upon the vessel, and those obtained after the administration of ergotamine, are identical, and I would feel that this is of some significance.

The effect of tobacco upon the induction of anginal attacks has been commented upon frequently. Huchard²¹ in his chapter upon Toxic Angina Pectoris, had a great deal to say about the effect of tobacco in causing attacks. Wilson and Johnston²² recently reported a series of cases with what would seem very clear evidence that the anginal attacks were caused by a vasomotor narrowing of the coronary arteries, precipitated by the smoking. Hobbs, working upon this problem, has found two cases where the electrocardiographic changes did not occur after atropine.

I spoke earlier of the possibility that vasomotor restriction of coronary flow, oft repeated over long periods of time, might eventually result in permanent degenerative changes in the heart muscle consequent upon temporary decrease in blood supply. Blumgart and his fellow-workers²³ have shown that arrest of the blood flow for as short a period as one minute in a single coronary artery led to electrocardiographic changes indicating anoxemia of the muscle. Arrest of the flow for from 25 to 45 minutes produced histological changes in the muscle.

Hall, Ettinger and Banting²⁴ have shown that prolonged stimulation of the vagus, continued over several months of time, produced changes in the heart muscle of the dog, comparable to chronic clinical degenerative changes in man. Intrinsic changes in the vessel walls of the dog's heart did not occur to any significant degree. It would seem very reasonable to assume that similar changes occur clinically in man, or as a result of repeated extrinsic factors restricting the coronary flow for varying periods, over long time intervals.

The experiments of Hall and his associates were performed upon dogs with normal heart muscles and normal vessels. When the heart of man is hypertrophied from any cause, whether as a result of previous valvular damage, or as a result of hypertension, there is an increased bulk of heart muscle without a proportionate increase in blood supply to provide for the increased needs. In such hearts, with a blood supply already insufficient, or barely sufficient, and possibly with intrinsic vascular changes, a further restriction of coronary flow because of extrinsic

factors may produce serious changes much more rapidly and much more certainly than in a normal heart.

I am sorry to have burdened you with so long a discourse, but even then it is too brief and incomplete to show adequately the importance of the extrinsic factors which tend to decrease the coronary flow. I hope that what I have said has carried some small degree of conviction as to the importance of these factors in diagnosis and therapy.

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PULMONARY CONGESTION AND EDEMA *

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I N attempting to discuss the complex problem of pulmonary congestion and edema within the time allotted, I thought it advisable first to present certain general considerations and conclusions. Then I shall demonstrate these points more specifically with the help of lantern slides. The proposed discussion will be based mainly on experiences gained in the study of man. No attempt will be made to deal with the extensive and controversial animal experimentation.

Congestion and edema of the lungs are two important morbid states, which develop in the course of many diseases. Whenever they appear they are responsible for serious symptoms and for secondary complications. Thus, the majority of the symptoms and signs of congestive heart failure, such as dyspnea, orthopnea, cough, asthma, certain types of thoracic distress, cyanosis, rales, hemoptysis and hydrothorax, depend partly or entirely on such secondary derangements within the pulmonary circulation.¹

It is only recently that the study of the normal and abnormal states of the human pulmonary circulation has become possible. As a result, valuable information has been accumulating not only on the pathologic physiology of the pulmonary circulation, but also on the better interpretation of structural alterations and of symptoms referable to the lungs.

The pulmonary (lesser) circulation may be looked upon as a counterpart of the capillary system of the greater circulation. As the huge capillary bed of the lungs is freely exposed to the atmospheric environment, it is not surprising that under certain conditions it undergoes serious disturbances. It is, indeed, remarkable that pulmonary edema does not develop under stress more frequently.

Usually the function of the blood capillaries is to send to or remove from the tissue fluids in which cells live, dissolved substances and fluids.

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However, to a great extent the opposite is true, as far as the pulmonary capillaries are concerned. Their primary functional task is to allow the blood flow through the alveolar wall, while the respiratory exchange takes place, without change in fluids or solutes. This difficult homeostatic state of the pulmonary capillary circulation is maintained by a combination of physiologic and structural arrangements. Thus the relation of the low pulmonary capillary pressure to the osmotic pressure of the blood results normally, as far as the alveolar space is concerned, in a force of absorption, rather than of transudation. As early as 1873 Colin² demonstrated that as large an amount as 21 liters of water can be administered intratracheally to the horse in the course of three and a half hours without ill effects. Further, the pulmonary capillaries are unusual morphologically, in the sense, that they are "reinforced" by special layers of tissues which make diffusion of substances and transudation of the fluids difficult. Hence, although the minute vessels of the lungs are practically in contact with the air, nevertheless the blood is separated from the air by four delicate layers: (a) an endothelial layer, (b) two basement membranes, and (c) an epithelial layer. No lymphatic vessels or circulation exist within the alveolar walls, although the rest of the structures of the lungs are richly supplied with lymphatics. Actually the lymphatic network of the lungs is more dense and prominent than that of the liver, spleen, and kidneys. In view of the fact that conditions associated with edema of the alveolar wall are also associated with engorgement of the lymphatics and presumably with the lymphatic flow, it is assumed that the tissue fluids of the alveolar wall find their way to the lymphatics of the atria.

Under normal conditions the total cross-sectional width of the layers separating the circulating red blood cells from the alveolar air is less than one micron, hence gasses diffuse through the alveolar wall with ease. Each pulmonary capillary is about $\frac{1}{2}$ to 1 millimeter in length and about 10 microns in diameter. Therefore, usually but a single row of red cells passes through the capillaries. As long as the alveolar wall remains elastic the pulmonary capillaries stretch easily. This is clearly indicated by the fact that histiocytes and large reticulo-endothelial cells, bulging with lipoid material, can pass through the normal pulmonary capillaries. Further, in heart failure with an increase of the pulmonary capillary pressure, the capillaries may enlarge 10- to 30-fold, and may assume aneurysmal dilatation. The surface of the pulmonary capillary bed has

been estimated at about 140 square meters (Hüfner). Under basal conditions about 3 to 3.5 liters of blood flow through the pulmonary capillaries per minute. In healthy persons the velocity of blood flow through the pulmonary circuit from the right to the left ventricle is 5 to 10 seconds, and anatomic and physiologic considerations indicate that the length of the pulmonary pathways is about equal. The average amount of blood at rest in the normal human lungs is about 500 to 800 cc. Under physiologic stress variations in the volume of blood flow and in its velocity *do not* parallel one another. In heart disease associated with pulmonary congestion there is a considerable degree of increase in the cross-sectional area of the capillary bed. Hence in these cases the disproportion between changes in the volume and velocity of the pulmonary blood flow is particularly great; and normal cardiac output may be associated with a slowing of over one hundred per cent of the normal velocity of the pulmonary blood flow. The shapes of dye concentration curves indicate that in the presence of pulmonary congestion caused by heart disease, in contrast to the normal pulmonary circulation, the velocity of blood flow varies in different parts of the lungs. It is considerably slower in the base than in the upper parts.

Neither the distribution nor the functions of the pulmonary nerves are clearly understood. The vagi and the sympathetic nerves form numerous plexuses and nerves along the bronchial tree and pulmonary vessels. According to Miller,³ the nerves end in the walls of the atria and in smooth muscles of the smallest bronchioles. Olkon and Joannidas⁴ and Sternberg and Tamari,⁵ on the other hand, have claimed that the capillaries of the lungs are innervated. It is doubtful whether the pulmonary capillaries are under active nervous control, in the orthodox sense. Chemical agents, on the other hand, liberated by nervous stimulation, may well influence the capillaries directly or indirectly.

The physiologic mechanism as well as the treatment of pulmonary edema is *not uniform* in all cases. The usual clinical causes of pulmonary congestion and edema are: (a) changes in the pulmonary circulation caused by heart failure (coronary disease, arterial hypertension, aortic insufficiency or stenosis, mitral disease and diffuse myocardial disease); (b) systemic or pulmonary diseases associated with pronounced changes in the pulmonary hemodynamics and/or with capillary damage (pulmonary infarcts, pneumonias, drowning, irritant gasses); (c) diseases associated with retention of fluids in the tissues (beriberi, glomerulone-

phritis, and toxemia of pregnancy). Frequently in the causation of pulmonary edema the physiologic causes are combined. Such is the case in certain instances of pneumonia, beriberi, uremia, toxemia of pregnancy, thyrotoxicosis and circulatory shock. It has been known for a long time that certain diseases of the central nervous system (cerebral trauma, cerebrovascular accidents, and encephalitis) are frequently associated with pulmonary edema. The pathogenesis of this edema is not clear. It is probable that in these so-called "neurogenic" pulmonary edemas, the underlying mechanism is a disturbance of the vasomotor system with secondary changes in the functional capacity of the heart, in the greater and in the pulmonary circulation. In this sense neurogenic factors induce pulmonary edema indirectly.

In general it may be said that *the formation of pulmonary edema follows the same biologic laws as the development of peripheral edema*; although the relative significance of the factors involved is apparently not the same in these two types of edemas. Changes in capillary pressure, blood flow, protein content of the blood, permeability of the capillary membranes, are the chief factors operative in the formation of pulmonary edema. Combination of high capillary pressure, stasis (ischemia) and anoxia are particularly important in the causation of pulmonary edema of heart disease. It is probable that in slow blood flow, the active factors are chemical in nature. Specific evaluation of factors causing changes in the permeability in the pulmonary capillary wall is particularly difficult; but in this respect again the situation is not unlike that in the capillaries of the greater circulation. It appears that if once the activity of causative factors reaches a certain critical point, edema formation can progress with great rapidity. The longer the duration of the pulmonary edema, the more difficult it becomes to reestablish the normal physiologic state. The edema fluid may be of low or high protein content. As a rule the edema fluid of cardiac origin is low in proteins (transudate), while that caused by infections or of chemical origin is high (exudate). As histologic observations have shown, the pulmonary capillaries are relatively easily permeable to red and white cells. The edema fluid both of the alveolar space and of the lymph frequently contains red cells. Pulmonary edema may be acute or chronic. Acute pulmonary edema may be transient or fatal. Both pulmonary congestion and edema may be diffuse or localized. One of the best examples of localized pulmonary edema is that occurring in pneumonia. This

type of edema is caused by gross damage done to the capillary layers by the bacteria. The high protein content of alveolar fluid indicates that here we are dealing with an inflammatory exudate.

In heart disease congestion usually precedes pulmonary edema. The edema may be either *pericapillary* (*interstitial*) or *intra-alveolar*, or a combination of the two. Usually, however, the intra-alveolar edema of heart disease is preceded by pericapillary edema. The pulmonary edema caused by infectious diseases, chemical agents and perhaps nervous mechanisms, on the other hand, often develops without any preceding congestion, and results instead from changes in the permeability of the layers of the alveolar wall ("primary" intra-alveolar edema).

On the basis of studies conducted in man during the past fifteen years,^{1, 6-21} an attempt has been made to correlate symptoms, physical findings, and roentgenological characteristics, with physiologic and histologic findings. A few of the pertinent conclusions are as follows:

1. Failure of the pulmonary circulation occurs frequently in the presence of an adequately maintained greater circulation. Thus, dyspnea, orthopnea, pulmonary edema, and low vital capacity of the lungs can be associated with normal cardiac output, normal arterial and venous pressure, and normal utilization of oxygen by the tissues.

2. Pulmonary engorgement is usually associated with some degree of edema of the alveolar wall, causing thickening and rigidity of the alveolar sac. If the edema has existed for but a short period, rapid reabsorption of the edema fluid develops provided the normal physiologic relationships are reestablished. Measurements of air spaces in cardiacs with acute pulmonary congestion indicate that changes in the lungs are responsible for the creation of an acute functional emphysema-like state.

3. Pericapillary edema of the alveolar wall can lead rapidly to deposition of collagen. Judging from the behavior of the lungs in preëclampsia and eclampsia of pregnancy, collagen may be deposited in the edematous alveolar wall over a period of weeks, and subsequently, presumably, this collagen can become absorbed. If, however, the edema persists, permanent organic changes can occur in the alveolar wall. The advanced manifestation of the structural changes consists of fibrosis of the alveolar wall with obliteration of the capillary bed and with cuboidal changes in the epithelial cells. Thus, heart disease can cause first physiologic (reversible) and subsequently organic (irreversible) lung disease. The latter is seen in advanced cases of mitral stenosis. In these patients, not

only are the capillaries markedly widened, but the alveolar wall is considerably thickened. This is the chief cause of central (pulmonary) cyanosis in these patients. In some cases with an advanced type of mitral stenosis rupture of the capillaries with aneurysmal enlargement can be responsible for serious and at times fatal pulmonary hemorrhage.

4. In the presence of an advanced degree of mitral stenosis, dilatation of the pulmonary capillaries over the upper half of the lungs may not be accompanied by an appreciable degree of pericapillary edema. This observation suggests that increased intracapillary pressure alone, without slowing of the blood flow or anoxia, is not necessarily the primary factor in the causation of pulmonary edema.

5. A large amount of pericapillary (interstitial) edema may be present in the lungs without intra-alveolar edema and without pulmonary rales. This situation is responsible for the clinical fact that patients with left ventricular failure, in particular, can have dyspnea, orthopnea and low vital capacity of the lungs without rales.

6. In primary intra-alveolar edema the structure of the alveolar wall remains normal, and yet intra-alveolar filtrate diffuses freely through all layers of the alveolar wall. At times, with the edema fluid, large numbers of red cells pass through the alveolar wall. The physical signs of this type of edema consist of extensive bubbling rales. Diffuse intra-alveolar edema may be unilateral or may involve but one lobe.

7. The term "left ventricular failure," or more properly "chronic left ventricular failure," does not imply that under usual conditions the output of the two ventricles is unequal. This would be a physiologic impossibility. These terms simply indicate that there is severe impairment of the reserve of the functional capacity of the left ventricle as compared with that of the right ventricle. As a result, under *physiologic stress*, serious imbalance between the functions of the two ventricles is prone to occur. In the understanding of paroxysmal dyspnea (cardiac asthma) and transient pulmonary edema associated with heart disease, it is essential to appreciate that a disproportion in the functional activities of the two ventricles can lead to active engorgement and gross disturbance of the pulmonary circulation within a few seconds or minutes. If following such temporary imbalance, the vitally essential balance between the ventricles, as far as equal output of blood is concerned, is reestablished, the engorgement accompanied by dyspnea, orthopnea, and edema will, nevertheless, continue to persist, because the previously

accumulated excess of blood and edema now remains trapped within the pulmonary circuit. Under such circumstances for the relief of the attack, it is essential that the left ventricle temporarily throw out more blood from the lungs than the right throws in. Otherwise, the excess volume within the pulmonary circuit has to diffuse into the lung tissues, lymphatics, and alveoli, before the dyspnea and orthopnea will disappear. Most effective measures in the treatment of acute left ventricular failure with dyspnea, asthma, and pulmonary edema bring about temporary improvement in the function of the left ventricle. This is accomplished by decreasing either the arteriolar resistance or the inflow to the heart or both. Studies conducted by us indicate that improvement in the pulmonary circulation is often accomplished promptly, while disappearance of edema and stiffening of the lungs, takes a longer time. We have observed both in patients with cardiac asthma and in those with other types of heart disease, that the restoration of the pulmonary hemodynamics long preceded the disappearance of the so-called "functional circulatory emphysema" caused by changes within the alveolar wall proper.

8. Acute left ventricular failure or transient disproportion between the two ventricles, may be associated with normal, elevated, or low arterial pressure of the greater (peripheral) circulation. It is particularly important to realize that the syndrome of acute heart failure or "cardiac shock" is accompanied by a clinical picture similar to or identical with that associated with acute circulatory collapse or shock of peripheral vascular origin. Thus, in cardiac shock such as occurs in coronary thrombosis, pulmonary edema depends on failure of left ventricular function, notwithstanding the fact that the arterial pressure is low and the clinical picture is one of shock.

9. In some instances of left ventricular failure caused by arterial hypertension, attacks of paroxysmal dyspnea are associated with acute pulmonary engorgement and with progressive histologic changes such as deposition of fibrin and connective tissue, which in the past have been erroneously looked upon as "organising pneumonia."

10. Attacks of pulmonary edema may be associated with fever and leukocytosis, the latter reaching as high a degree as 40,000 white blood cells per cmm. of blood. Patients have been observed, in whom each attack of paroxysmal dyspnea has been associated with fever of one to three days duration.

11. Roentgenologic studies of pulmonary congestion and edema indicate that the distribution of edema varies in different types of congestive failure. In "general" failure of the heart, the congestion and edema are usually dependent ("basal")—(passive engorgement). In pure left ventricular failure, the congestion and edema are often hilar and perihilar, with progressive fan-shaped distribution (active engorgement). The base of the lungs often remains relatively normal. It is of interest, that usually the congestion and edema start over the right lung and remain more intense over this side. This is significant in view of the fact that right hydrothorax usually precedes left hydrothorax.

12. During and immediately following an attack of cardiac asthma or pulmonary edema, as shown by roentgenograms, various bizarre-shaped distributions of edema can appear. These changes may disappear within 24 to 48 hours. Obstruction of lymphatic drainage is one factor which influences the persistence of edema within certain areas of the lungs. At times the appearance of the roentgenogram may be similar to or identical with that observed in tuberculosis or pneumoconiosis.

13. Accumulation of edema in the large lymphatic vessels close to the lung roots can be responsible for a large cyst-like accumulation of fluid, imitating the shadows caused by aneurysms or neoplastic diseases.

14. In rare instances of mitral stenosis small, persisting, diffusely-scattered, dense areas are present in roentgenograms of the lungs. Such a roentgenogram imitates that found in miliary tuberculosis or in sarcoïd. The areas described are formed by hemosiderin pigment deposits and surrounding tissue reactions.

15. The roentgenologic differentiation of pulmonary edema, infarction, pneumonia and fibrosis is often difficult. Pulmonary infarction is often associated with local or generalized pulmonary edema.

16. In the treatment of pulmonary edema the specific pathogenesis is to be taken into consideration. In the usual paroxysmal dyspnea and edema of cardiac origin factors which relieve pulmonary engorgement and stasis and improve the functional capacity of the left ventricle are the effective measures.

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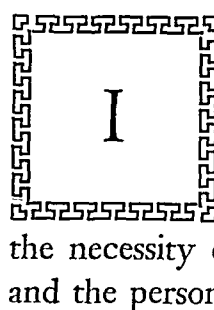
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OXYGEN SUPPLY SYSTEMS FOR MILITARY FLYING*

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I N preparation for writing this paper, I took occasion to refer to an article which I read nearly nine months ago. As a matter of fact, it has not yet been published. In it I presumed to define in some detail the requirements of military oxygen supply apparatus in conformity with the necessity of meeting the requirements of the airplane, the service and the personnel.

The principles expressed at that time are as sound today as they were then but in re-reading it a few days ago, I was astonished at the progress which has been made since then. There was no intent then to create the inference of prophesy but, in retrospect, development of oxygen equipment and description of desiderata for such equipment have followed very closely the principles which were generally accepted then. Nor were the general principles then expressed considered as the implantation of seeds for the fruition which is presently to be garnered. Nevertheless, it is timely to describe equipment as it exists or is being developed today and to reiterate requirements in much more exact terms than was possible that short time ago.

The credit for the advances made cannot be given to any single individual or group of individuals. Contributors include service personnel, private research groups, federal agencies and the industry itself. No small measure of credit is due the National Research Council's Committee on Aviation Medicine. A far-sighted, comprehensive plan for investigation, a thorough knowledge of goals to be attained and the methods to be employed in reaching them, an unremitting zeal in adding to their knowledge by all possible means and an unstinted patriotic application of time and effort have done much to make our present status what it is. Itself without funds, the National Research Council's Committee on Aviation Medicine has guided and urged other better endowed agencies in their efforts. Specifically, the formulation of desiderata and criteria

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for testing proposed oxygen equipment is a direct and distinct contribution of the Committee.

Before beginning a detailed description of the types of oxygen equipment for military flying, it may be well to review briefly the reasons for its use. For this purpose, I have decided to show two charts which illustrate the cardinal reasons for the use of oxygen and the special requirements interposed for military aviation.

Chart I shows very graphically in parallel column the important meteorological conditions encountered in ascending to higher altitudes.

Chart II shows the total barometric pressure prevailing at increasing altitudes, the partial pressure of oxygen at normal percentage at those altitudes, the arterial saturation under these partial pressures and the arterial saturation at these altitudes when 100 per cent oxygen is breathed.

It will be noted that while breathing normal air the arterial saturation is significantly reduced even at 10,000 feet and is progressively reduced as the altitude increases. At 20,000 feet the arterial saturation is only 60 per cent. This shows why normal efficiency cannot be expected at this altitude breathing normal percentages of oxygen.

When the deficiency in partial pressure using normal percentages is made up by providing 100 per cent oxygen in a breathing apparatus, the arterial saturation continues to be adequate for physical and mental efficiency up to 30,000 feet at least. However, please note that as we approach 40,000 feet, the total barometric pressure drops so low that, even if the inspired mixture is made up of nothing but oxygen, its partial pressure is inadequate to preserve 100 per cent arterial saturation. Above these altitudes, arterial saturation can only be maintained by raising the total barometric pressure by pressurizing cabins or suits.

But replacing the deficiency of oxygen to avoid anoxia is not the complete picture. In addition to the problem of anoxia, per se, we are beset by the ogre of aeroembolism which rears its ugly head in increasing ferocity. With increasing rates of climb to higher and higher altitudes and capability of continuing at these altitudes for increasingly longer periods of time, we find that the contribution which oxygen supply apparatus can make to the solution of this problem becomes increasingly important. Without discussing aeroembolism in any detail, suffice it to say that the only practical solution we have today is the augmentation of nitrogen elimination provided by breathing pure oxygen for

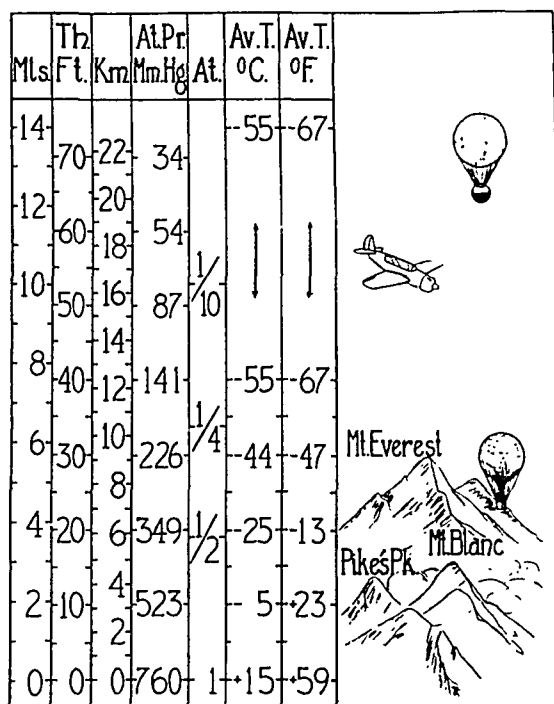


Chart I

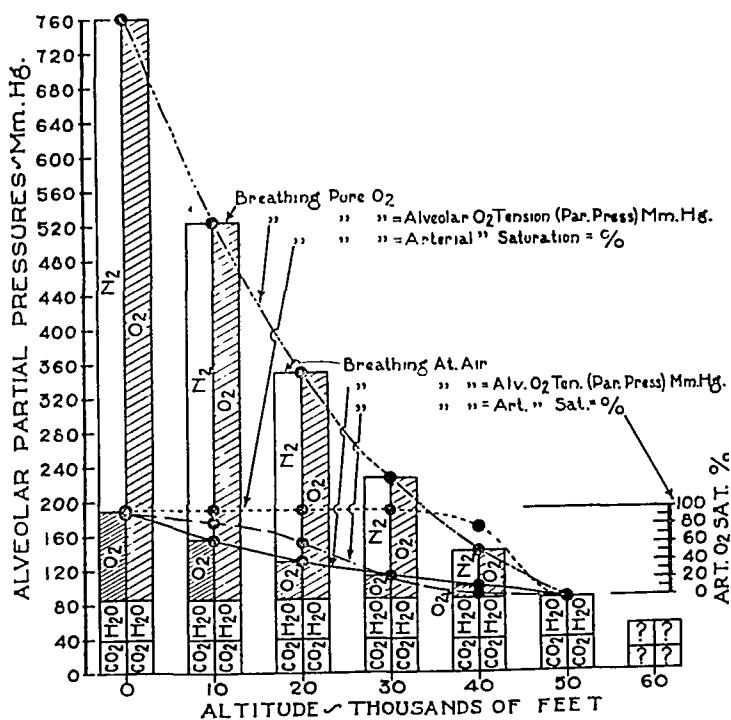


Chart II

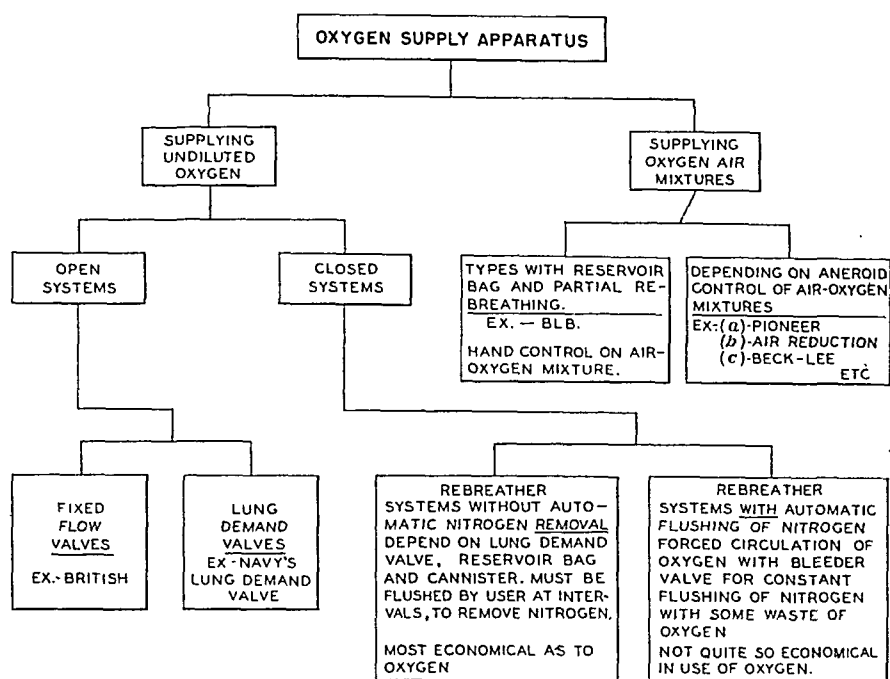
as long as possible before attaining 30,000 feet. This means, for the purposes of this evening's discussion, that for military missions in which aeroembolism is a hazard, oxygen equipment must be capable of delivering 100 per cent oxygen from time of take off.

This brings us to the description of the types of oxygen equipment which can find application in military aviation. In the first place, it is well to reiterate that it appears undesirable to settle upon a single type of apparatus for all purposes. This is apparent by considering the wide range of variations in the need to which military aircraft are put.

On the one extreme is the very fast, rapidly climbing high altitude interception fighter. Those small planes can take their pilots to altitudes at rates which make aeroembolism an important likelihood. But their total time in the air may not exceed two hours. Oxygen must be supplied these pilots completely unadulterated from the ground up, from before take off. The nature of the mission precludes any adjustment or attention during the flight. They must be positive, simple and generously adequate. The whole flight will require but a relatively few liters of oxygen under constant flow conditions. It may be that the most practicable and reliable means of supply for this type is a constant flow system which provides a positive pressure at the face, thus reducing the necessity for close fitting masks.

At the other extreme are the long range patrol bombers with a multiple crew, never or seldom attaining to extreme altitudes yet flying for long periods at moderate oxygen altitudes. In this type, economy of oxygen is of the essence. Aeroembolism is not a problem. The crew is large enough to permit considerable frequent and delicate adjustment. Adjustment must be capable of providing for the range of activity between sedentary co-pilot and ammunition-wrestling gunners. Most of the crew may be comfortably warm. An exposed bombardier or gunner may be exposed to extremely low temperature on occasion. For this type, we may find a place for elaborate installation with facilities to adjust for wide ranges of physical exertion and altitudes, designed and operated on the basis of a cardinal need for economy.

Between these extremes there are variations in types of aircraft where oxygen installation must be judged on the basis of rate of ascent, to what altitude, for how long a flight, with what degree of exertion or cold and with what opportunity for adjustment and control of equipment. Indeed, it appears unreasonable to expect a single type of equip-



PREPARED BY LIEUT COMDR LEON D CARSON (M C) U S NAVY

Chart III

ment to meet all requirements without some sacrifice somewhere. The analogy may be far fetched but the situation might be compared to installing the same motor in a jalopy and in a 10-ton truck. But it is equally true that there are many reasons for keeping the number of types at a minimum. Procurement, maintenance, indoctrination, familiarity, serviceability and uniformity all point to the desirability of a very limited number of types. The balance between these two concepts must be struck on a fulcrum which is ever changing as types of aircraft and tactical uses vary in relative concentration. The range of choice is apparent when we consider the types of equipment available.

Oxygen supply apparatus are divided, first, into (a) those which supply undiluted oxygen and (b) those which supply oxygen and air mixture.

UNDILUTED OXYGEN SYSTEMS

Those supplying undiluted oxygen are divided into (1) open systems and (2) closed systems.

OPEN SYSTEMS

The open systems are by far the least economical of oxygen. They are the most dependable to furnish 100 per cent pure oxygen. In one case, the oxygen is supplied by fixed flow valves with no control over rates of flow. These provide a constant flow of pure oxygen through the breathing mask. They do not require expiratory leak-proof masks, have no valves to provide resistance to breathing, are not so subject to freezing as those with expiratory valves, are very reliable and are very simple in construction and operation. They are very wasteful of oxygen. In another case, operation depends upon the lung demand principle. A system of valves is incorporated to permit the flow of oxygen only during inspiration. During expiration and the pause between expiration and inspiration, the supply of oxygen is cut off. Because of this intermittent flow, this type is more economical than the fixed flow valve type but it makes no provision for the percentage of oxygen not absorbed by the lungs, more than 85 per cent oxygen being exhaled to the open air.

The lung demand type interposes a number of stipulations which require very careful control and test criteria. They must function throughout a wide range of barometric and temperature variation. They must provide adequate partial pressure of oxygen up to the physiological ceiling. They must be capable of furnishing adequate rates of flow even under extreme exertion and peaks of inspiratory demand. They depend on both inspiratory and expiratory valves which must introduce a minimum resistance and must not freeze at very low temperature and moderate wind velocities. The lung demand type requires an absolutely leak-proof mask. If there is an inspiratory leak there will be dilution by ambient air. If there are expiratory leaks, there is increased chance for frostbite and loss of economy through failure to close the lung demand valve. They must be provided with emergency by-passes. The number and exactitude of these stipulations has prompted the National Research Council's Committee on Aviation Medicine to formulate an extensive set of desiderata and test criteria. If time permitted, it would be interesting to describe these in detail.

CLOSED SYSTEMS

The closed systems for supplying undiluted oxygen are essentially

rebreathers which provide for conservation of unabsorbed exhaled oxygen. There are two general types. In one the system is entirely closed except for a manually operated exhaust valve. Exhalation is through a cannister which absorbs oxygen and moisture (and incidentally generates a small amount of oxygen) into the breathing bag. As the rebreathing volume is depleted by absorption of oxygen in excess of that generated, the deficiency is made up by the opening of a valve from an oxygen supply system. This may be an integrally attached flask or a central low pressure supply system which may be tapped at a number of positions distributed throughout the aircraft. This is by far the most economical of all oxygen breathing apparatus. It has one significant drawback. There is no provision for automatic exhaustion of nitrogen which accumulates in the system during ascents. As the ambient barometric pressure decreases, nitrogen will appear out of solution in the cells, tissue fluids and blood into the expired air. Even though no nitrogen is introduced from the outside into the completely closed system as much as a liter may accumulate in the breathing circuit in an ascent to 18,000 feet. This accumulated nitrogen is disposed of by periodic flushing of the entire system by exhalation through the manually controlled exhaust valve. This requires conscious attention on the part of the user because there is no means of knowing the exact amount of dilution by oxygen. Also, as ascents are made to higher altitudes there will necessarily be dilution by nitrogen and this system has, therefore, a "built-in ceiling."

Another type of rebreather provides for the elimination of nitrogen by constant bleeding of a portion of the rebreathing volume. For this reason it is not so economical as the completely closed circuit type. The oxygen is forcibly circulated by an injector in the oxygen supply line. It circulates under slight positive pressure past the bleeder valve through a carbon dioxide absorbent, thus maintaining a high percentage of oxygen. Tidal air variations are provided for by a breathing bag. Preliminary tests of a model of this type gives considerable promise of its efficiency and adaptability to military flying.

Both types of rebreather have one common, very desirable feature. They supply warm oxygen. The chemical action of the carbon dioxide absorption produces considerable heat which extends into the inspired portion. At altitudes where the temperatures are low, this is a tremendously comforting thing for the user.

By the same token, they have one common serious impediment. They will not start at low temperature. No carbon dioxide absorbent will begin action in the presence of cold dry carbon dioxide alone. If the apparatus becomes chilled by not being used before cold altitudes are encountered or by climatic conditions, the exhaled moisture will condense before the exhaled oxygen and carbon dioxide reaches the absorbent. Under these circumstances the chemical reaction involved in the absorption of carbon dioxide will not begin spontaneously. This can be obviated by exhaling directly into the absorbing cannister or by artificially heating the exhaust tubing. Both of these introduce engineering and service complications. Nevertheless, the promise of economy of oxygen in the rebreather type of oxygen equipment warrants accelerated efforts to overcome this impediment.

OXYGEN-AIR MIXTURE SYSTEMS

In the interest of economy, a number of oxygen breathing apparatus have been and are being developed on the general principle of permitting dilution by air at altitudes at which 100 per cent oxygen may be unnecessary. These are mentioned in the first division in contrast to those supplying undiluted oxygen. Here, again, we find a dichotomy into those which incorporate anaeroid control of the amount of dilution by ambient air and those which depend upon varying rates of flow to provide an adequate concentration of oxygen.

ANAEROID CONTROL TYPE

The anaeroid control type is essentially a lung demand type which permits decreasing dilution of ambient air up to a minimum altitude above which only 100 per cent oxygen is acceptable. For the kinds of flying to which this type is adapted, it need not supply oxygen under 8,000 feet but must supply pure oxygen at 25,000 feet and over. Within this range the increments of oxygen and air may vary, being governed on the one hand by a minimum partial pressure of oxygen of 70 mm. mercury and on the other hand by economy of oxygen.

Several models of this type of equipment are being developed and tested. They vary in certain details such as anaeroid control of the oxygen supply, the air supply or both; methods of mixing; reduction of pressure from high or low pressure supply lines; means of providing for peak inhalations, etc., but, essentially, they embody the same general

principles. To find wide or general applications, they must be provided with means to shut off the dilution and supply pure oxygen at all barometric pressures.

RATE OF FLOW CONTROL TYPE

Any type of diluter supply system which depends upon varying rates of flow of oxygen to a breathing bag to provide for adequate concentration of oxygen at varying altitudes and exertion and does not incorporate either manual or automatic means for controlling the amount of air intake, has certain basic fallacies. If the rate of flow is adequate to provide for high altitudes and moderate exertion, it becomes essentially a free flow apparatus and economy is lost. If the amount of air dilution is unknown or unpredictable it will expose the user to the insidious influence of anoxia which may become poignant at any time as a sudden and catastrophic collapse.

This discussion is purposely avoiding inclusion of the different means of supplying oxygen to the aircraft, whether liquid or gaseous, high or low pressure flasks or hypothetically possible means of generation or compressing in the aircraft. These are essentially engineering problems. Two cardinal requirements must be observed: the oxygen must be pure and it must be dry. A detailed discussion of oxygen masks and helmets has also been scrupulously avoided. This subject is too interesting and intriguing to be sketchily included in this paper which has already consumed too much time.

TYPES BEING USED

Just a word about the types being used by air services today. From information which reaches us through liaison channels, it may be said that, in general, European combatants are using models of the following types of equipment: The R.A.F. is using a type of free flow apparatus which can be adjusted for different altitudes and does not require a leak-proof sealed mask. They are making rapid progress in the development and extension to service of more economical equipment, better fitting masks and means for providing oxygen. The Luftwaffe has profited by their years of peace-time preparation and has the best equipment in service use today. They have concentrated on a lung demand type which is characteristically well designed and built, is very efficient and foolproof, has been perfected by years of meticulous research and

extreme service proving and could be profitably copied by any air service. In our service we are well equipped with oxygen apparatus. The Navy uses a lung demand type and the Navy rebreather. They are quite satisfactory. The Army Air Forces are using a rate of flow regulator which is meeting service needs.

We have had an excellent year of accelerated research, development and testing of improved oxygen equipment. In a subject as important as oxygen supply apparatus for military aviation, there should be no let-up in this program of improvement.

Tremendous strides have been made, thanks to the characteristically American kind of all out service of brains, sweat, ingenuity and productivity. We are prepared to write the detailed specifications for the immediate mass production of the best types of oxygen equipment to meet the needs of our growing flying services. Those who have contributed to this development and have made our confidence justifiable, have every reason to be genuinely proud.

SOME RECENT ADVANCES IN
DRUG THERAPY *

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THE subject for discussion this afternoon is "Some Recent Advances in Therapeutics." It was decided that such an assignment could be turned to the best advantage of the listeners by reviewing the majority of important therapeutic advances rather than by selecting only a few topics for detailed discussion. In addition to answering the perennial question, "Well, what is new?", an attempt will be made to answer the more important query, "What is it worth?" With this plan in mind, it is of interest to survey briefly the newer advances in drug therapy by arranging them in groups according to their relative clinical value. For the purpose of the present discussion, new drug therapies, or new ways of employing old drugs, have been arranged in four groups—according to the following scheme: In Group I are included those advances which are now generally accepted and of proven worth. In Group II are listed those advances which are very promising, but which require further clinical investigation before being widely employed in daily practice. In Group III are placed what, in the reviewer's opinion, are questionable therapies, requiring further work to delineate their proper status. In Group IV are listed those therapies which, in the reviewer's opinion, either hold very little promise, or which are irrational and destined for eventual discard. Some medical toes are bound to be tread on in attempting any such classification as this, and it must be emphasized that the selection is purely one person's appraisal. It is to be regretted that a detailed presentation of the reasons underlying each particular classification cannot be given here.

GROUP I

In Group I are tabulated those recent advances in drug therapy of

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TABLE I
RECENT THERAPEUTIC ADVANCES OF PROVEN WORTH

| | | |
|---|--|---|
| Newer sulfonamides (sulfadiazine, sulfaguanidine) | Antispasmodic atropine substitutes (syntropan, trasentin, etc.) | Dihydrotachysterol (in parathyropriva) |
| Local use of sulfonamides | | Desoxycorticosterone (in Addison's disease) |
| Prophylactic oral use of sulfonamides | Thiamine (in deficiency neuritis, C-V states, ophthalmoplegia) | Quinine (in myotonia congenita) |
| Dilantin (in epilepsy and in psychic equivalents) | Nicotinic acid (in pellagra, deficiency encephalopathy) | Papaverine (in peripheral and pulmonary arterial embolism) |
| Blood substitutes (human plasma) | Riboflavin (in deficiency cheilosis, keratitis) | Heparin (in blood vessel surgery; to prevent thromboses and embolism; etc.) |
| Newer epinephrine preparations (inhalation, 1%; oil solution, 0.2%) | Vitamin K (in hemorrhagic diatheses due to a prothrombin deficiency) | |
| Theophylline ethylene diamine (in bronchial asthma) | | |

proven worth which are to be recommended for use in daily practice (Table I).

Newer Sulfonamide Therapy. At the head of the list appear the newer sulfonamide therapies. These have been so adequately dealt with in the current literature that it is not intended here to discuss them in any detail. *Sulfadiazine* and *sulfaguanidine* are the latest valid additions to the sulfonamide family. The *local* use of the entire group has come into considerable prominence within the last year and the value of this local therapy for medicine and surgery is difficult to exaggerate. Somewhat overshadowed is the fact that there are certain valid *prophylactic* uses for *oral* medication with sulfonamides, including the following conditions or diseases: the quiescent stage of rheumatic fever, scarlet fever contacts when the Dick test is positive, meningococcus carriers, compound fractures, extensive tissue injuries, peritonitis, otitis media, and burns, and prior to resections of the large bowel, urological operations, etc. With these sketchy remarks, respect has been paid to the most important advance of the century, and other drug therapies may now be considered.

Dilantin in Epilepsy. Dilantin has become firmly and deservedly entrenched in the treatment of epilepsy since its introduction in 1938, and possesses two outstanding advantages. First, dilantin is not a seda-

tive. Secondly, in addition to being at least as effective as bromide, phenobarbital, or the ketogenic diet in the control of grand mal, it is much more effective in the management of seizures of the psychomotor equivalent variety. Therapy with phenobarbital or bromide, as a rule, does not improve and may even aggravate symptoms in patients with psychic equivalents.

Human Plasma as a Blood Substitute. Of all the substitutes for human blood, the best is undoubtedly human plasma, either stored as such, or dried by the lyophilic method. Plasma is especially useful in the treatment of surgical and traumatic shock, in burns when loss of available plasma occurs, to combat hypoproteinemia, and as a temporary substitute for whole blood in hemorrhage, when whole blood is not immediately available. The plasma from different donors may be pooled and blood grouping of the recipient is then not necessary.

Newer Preparations of Epinephrine. In the symptomatic treatment of allergic states, and especially in bronchial asthma, the newer preparations of epinephrine have been of considerable assistance. These include the strong solution of epinephrine (1:100), inhaled after nebulization, and the solution of epinephrine in oil (1:500), injected subcutaneously or intramuscularly for prolonged therapeutic effects.

Theophylline in Bronchial Asthma. Not yet fully appreciated is the fact that within very recent years theophylline has been established as an effective bronchial antispasmodic. The mechanism of action of the drug is a direct spasmolytic effect on the bronchial smooth muscle. In asthma, it is usually administered by mouth for prophylactic purposes, or for control of symptoms in cases of moderate severity; but the drug often produces dramatic relief of status asthmaticus when injected intravenously. Theophylline with ethylene diamine, commonly known as aminophylline, is the preparation used for parenteral administration. This drug deserves wider clinical trial.

Synthetic Atropine Substitutes. Among the synthetic substitutes for atropine are several valuable antispasmodics—including novatropine, eumydrine, syntropan and trasentin. These are not exactly new drugs but only within the last two or three years has their clinical usefulness become generally appreciated. Novatropine and eumydrine retain much of the atropine structure, but syntropan and trasentin are more closely allied to the local anesthetics and actually have local anesthetic potency. Indeed, one may wonder whether the rapid relief of pain reported to

occur when these two compounds are given orally to patients with peptic ulcer may not, in some measure, be due to a local anesthetic action. All four agents have been found effective as antispasmodics and one or the other has been successfully employed in the symptomatic treatment of a variety of clinical conditions, including the following: pyloric stenosis in infants, spastic dysmenorrhea, ureteral colic, urethral spasm, hypertonic urinary bladder, spastic dyskinesia of the gall bladder and biliary ducts, and gastrointestinal spastic states. The common denominator of all these conditions is smooth muscle spasm. The agents mentioned relax the spasm without producing the unpleasant effects of atropine or other belladonna alkaloids, such as dry mouth, mydriasis, and changes in cardiac rate. In other words, more discrete therapeutic results are obtained. Syntropan and trasentin, in particular, produce their therapeutic effects by acting more directly on smooth muscle rather than by blocking cholinergic nerve impulses to smooth muscles. Before leaving this topic, it might be mentioned that quite recently certain obstetricians have been employing syntropan experimentally in labor, on the basis that dystocia of maternal origin is commonly due to functional spasm of the cervix, and that the drug might hasten cervical dilatation. Preliminary results obtained on several hundred patients indicate that labor may be shortened in duration by as much as 50 per cent, both in primipara and multipara, and apparently without deleterious effects on mother or infant. Obviously, this work requires careful study and confirmation before its status can be decided.

Thiamine. Thiamine, or vitamin B₁, is important in human nutrition. However, as a *therapeutic* agent, it should be employed chiefly when a definite deficiency is present, as in frank beriberi, in deficiencies characterized by certain forms of cardiovascular or gastrointestinal disorders, in symmetrical peripheral neuritis due to a lack of the vitamin and in Wernicke's ophthalmoplegia.

Nicotinic Acid. Nicotinic acid, another member of the vitamin B family, is similarly important in nutrition. However, as a *therapeutic* agent, it too should not be employed except in the presence of a specific and clear-cut nicotinic acid deficiency. As far as known at present, this occurs only in pellagra, and in an encephalopathy due to a deficiency of the vitamin.

Riboflavin. Riboflavin, another constituent of the vitamin B complex, is also essential in human nutrition. As a *therapeutic* agent, it should

be employed only when a definite deficiency is present. As far as is now known, such a deficiency of riboflavin manifests itself in man only in certain types of cheilosis, and in ocular disturbances consisting chiefly of a vascularizing keratitis, photophobia and impairment of visual acuity.

Vitamin K. Vitamin K is essential in human nutrition because of the role it plays in the production of prothrombin. In preventing or curing hemorrhagic diatheses due to hypoprothrombinemia, substances possessing vitamin K activity share qualitatively the same mechanism of action in elevating the plasma prothrombin. These substances are employed both prophylactically and therapeutically. In general, vitamin K is useful only in those hemorrhagic conditions in which abnormal bleeding is due to a low concentration of plasma prothrombin that is not occasioned by hepatic cell injury. This limits the employment of the vitamin to the hemorrhagic diatheses of certain types of hepatic and biliary disease, and to rarer instances of deficiency caused by faulty diet or absorption defects of the intestine other than those caused by a loss of bile. Vitamin K is employed prophylactically in all jaundiced patients in whom surgical procedures are planned, and also postoperatively if the prothrombin level was low before operation. Vitamin K is also a valuable agent in the treatment of hemorrhagic diseases of the newborn, and its administration to pregnant women prior to delivery has become routine. The commonly employed synthetic vitamin K preparation, 2-methyl-1, 4-naphthoquinone has been given the non-proprietary name "menadione" by the Council on Pharmacy and Chemistry of the American Medical Association.

Dihydrotachysterol in Parathyropriva. Dihydrotachysterol is a drug derived during the progressive irradiation of ergosterol. It is closely related to vitamin D. Within recent years, it has proven to be definitely useful in the management of patients with parathyropriva, having the advantage of being effective after oral administration. It is thought to exert its beneficial effect in raising the serum calcium and lowering the serum phosphorus through a mechanism of action similar to that of parathyroid extract.

Desoxycorticosterone in Addison's Disease. Desoxycorticosterone, one of the several adrenal cortical hormones, has proven of great value in the treatment of patients with Addison's disease, but its use necessitates considerable attention to the intake of sodium in order not to increase blood volume and thereby tax the circulation. It also appears

that desoxycorticosterone does not correct the defect in carbohydrate metabolism which exists in adrenal cortical insufficiency. For this reason, it may be necessary at times to supplement desoxycorticosterone with crude extract of the adrenal cortex, especially in patients who are quite ill or during periods of infection. For patients in an Addisonian crisis, the treatment of choice appears to be large amounts of adrenal cortical extract combined with solution of sodium chloride and sodium citrate injected intravenously. Adrenal cortical extract manifests both the electrolyte and the carbohydrate metabolic activities of the gland, and thus more nearly approaches complete replacement therapy than any single crystalline cortical hormone at present commercially available.

Quinine in Myotonia Congenita. Myotonia congenita or Thomsen's disease, a rare myopathy of unknown origin, is the pharmacological antithesis of myasthenia gravis. Recently, quinine has been found to be effective in the symptomatic treatment of the tonic spasm of skeletal muscles characteristic of the syndrome. The myotonic symptoms are quickly and sometimes entirely relieved, and the abnormal electrical reactions return to normal. The basis of the action of quinine is its ability to abolish the abnormal sensitivity of the myotonic muscle to mechanical stimulation. Therapy is not curative and benefit is obtained only as long as the alkaloid is given. It is of interest that quinine also is effective in obliterating the muscular rigidity in goats suffering from a form of congenital myotonia similar to that occurring in humans.

Papaverine in Arterial Embolism. Papaverine, the chief member of the benzyloisoquinoline group of opium alkaloids, has long been known in therapeutics, but only within recent years has it become firmly established as a valid and useful vasodilator in the emergency treatment of peripheral or pulmonary arterial embolism. For this purpose, it is injected intravenously in generous doses, and is often saving of life as well as limb.

Heparin in Prevention and Therapy of Thrombosis and Embolism, in Blood Vessel Surgery, etc. Within recent years, heparin has been sufficiently purified and reduced in price to the extent that it is now available for clinical use. It has been found of value in the therapy of a wide variety of medical and surgical conditions and procedures, including surgery of blood vessels, blood transfusion, prevention and treatment of thrombosis and embolism, thrombophlebitis, etc. The chemistry and mechanism of action of heparin have been considerably elucidated of

TABLE II

PROMISING NEWER THERAPIES REQUIRING FURTHER STUDY BEFORE
BEING GENERALLY EMPLOYED

| | | |
|--|--|--|
| Newer digitalis glycosides | Sobisminol (orally in syphilis) | Metopon (morphine substitute) |
| Benzedrine (in epilepsy, in parkinsonism) | Rotenone (in scabies, in chigger-mite dermatitis) | Gramicidin (in bacterial infections) |
| Picrotoxin (in barbiturate poisoning) | Benzyl benzoate (in scabies) | Penicillin (in bacterial infections) |
| Curare and erythroidine (in certain neuromuscular syndromes) | Phenothiazine (in enterobiasis) | Synthetic estrogens (stilbestrol) |
| Organic mercurial diuretics (by mouth) | Gentian violet (in enterobiasis, strongyloidiasis) | Progesterone (in threatened or habitual abortion, functional bleeding, dysmenorrhea, afterpains, etc.) |
| Short-term massive arsenotherapy (in early syphilis) | Atabrine (in giardiasis) | |
| | Plasma protein precursors (intravenously) | |

late, and the drug has at last become a valuable addition to the physician's armamentarium.

GROUP II

In Group II are listed those recent advances in drug therapy which are very promising, but which require further clinical study before being generally employed in daily practice (Table II). Likewise included are those recent contributions which, though purely in the experimental stage of investigation, show every promise of eventually proving to be therapeutically useful.

Newer Digitalis Glycosides. In recent months, the "native" glycosides of the lanata species of digitalis have received considerable attention, particularly in comparison with digitalis purpurea, the official U.S.P. source of digitalis. The three native glycosides of digitalis lanata are known as lanatosides A, B and C. When all three are employed, their combination provides an acceptable digitalis preparation for oral use, but this does not mean that such a preparation possesses any compelling advantages. Being water-soluble, lanatoside C has been employed for intravenous administration, but this route is warranted, as a rule, only when digitalis medication must be given quickly, that is, when minutes rather than hours determine the difference between life and

death. If the clinical findings obtained with lanatoside C are confirmed by further study, it is likely that this drug may then be added to the list of older and better known water-soluble, crystalline cardiac glycosides serviceable for parenteral administration, such as ouabain and strophanthin.

One can not help but take this opportunity critically to examine the advantages claimed for crystalline digitalis glycosides as compared to official galenical preparations, such as the powdered leaf and tincture. These claims include accuracy of dosage, a wider margin of safety (of lanatoside C, in particular), and the stability of purified crystalline preparations. While it must be admitted that the U.S.P. bioassay of digitalis allows much to be desired, no serious difficulty need arise therefrom in daily practice. In the last analysis, any *particular* product, galenical or purified, must be assayed on *each* patient, and individuals may vary considerably. The claim concerning the higher margin of safety of lanatoside C is especially misleading. All cardiac glycosides have the same basic action on the failing heart, namely, to increase the tone and force of contraction of the heart muscle. No good evidence exists that the toxic properties of digitalis-like drugs can be dissociated from their therapeutic actions. Therefore it remains to be proven that there are clinically significant variations in margins of safety between galenical digitalis preparations and purified glycosides. The toxic actions of all digitalis-like drugs are merely extensions of their therapeutic effects. Their potency or toxicity depends not on the degree of purification before being wrapped in the package, but on the amount of drug swallowed by the patient. The claim concerning stability is also misleading because all reliable studies show that galenical preparations of digitalis keep for many years without significant loss of potency. Finally, cost is an important factor, since most patients must take digitalis for life. By and large, the purified glycosides are much more expensive than U.S.P. digitalis leaf. Furthermore, even the lanatosides must undergo further chemical changes in the body before their active principles are released, and the patient's intestinal juices can release these principles from crude digitalis leaf as effectively as can the pharmaceutical chemist, and also much more cheaply.

For all these reasons, it is the opinion of the reviewer that in the overwhelming majority of patients with heart failure, one will find that U.S.P. powdered digitalis leaf is easy to administer, is readily absorbed

when given by mouth, is effective in its action on the myocardium, possesses an adequate margin of safety, is stable in potency, and that cumulation and elimination occur in the body at rates allowing complete digitalization at varying speeds and satisfactory maintenance of desired therapeutic effects for long periods of time. The burden of proof that any digitalis substitute or purified fraction is more valuable than U.S.P. digitalis still rests on those making such a claim. The general practitioner will do well for the present to select his therapeutic agents from U.S.P. preparations, and to leave the final evaluation of purified glycosides to the experimental investigator. Both he and his patients stand to gain thereby.

Benzedrine as an Adjuvant in Epilepsy and Parkinsonism. Benzedrine, one of the newer members of the epinephrine family, has recently been put to two promising uses, which, if substantiated by further clinical experience, will indeed represent definite therapeutic advances. Benzedrine differs from some of its immediate chemical relatives by having a powerful stimulant action on the central nervous system. This action is especially useful, for example, in the treatment of narcolepsy, and for the therapy of poisoning by central nervous system depressant drugs. Of particular interest at the moment is the fact that benzedrine may prove to be a valuable adjuvant to phenobarbital in the symptomatic treatment of epilepsy. Certain patients require large amounts of phenobarbital to control seizures. These large doses are likely to cause sufficient dizziness, ataxia and drowsiness to prevent the employment of phenobarbital. The concomitant use of benzedrine dissipates the untoward effects, and allows doses of phenobarbital to be employed which otherwise would be impossible. Apparently benzedrine used in this manner has no untoward effect on the character or incidence of the seizures.

Benzedrine is also a valuable adjuvant to belladonna alkaloids in the symptomatic therapy of postencephalitic parkinsonism. The mechanism of this action is not fully understood. In conjunction with atropine, scopolamine, stramonium or mixtures of belladonna alkaloids, benzedrine may allow a better sleep cycle, increased energy, subjective improvement in muscle strength and rigidity, and relief from oculogyric crises. Indeed, benzedrine appears to be almost a specific for oculogyric crises, the attacks being reduced in number and severity, or entirely disappearing. Best results are obtained when the disease is postencephalitic

rather than arteriosclerotic in origin, and when organic defects and personality changes are minimal.

Picrotoxin in Barbiturate Poisoning. Picrotoxin is another central nervous system stimulant. Until recent times, it was largely a laboratory curiosity. It is capable of lessening the degree of depression and of stimulating respiration in patients poisoned by anesthetic agents, especially barbiturates, against which it appears to be an effective pharmacological antagonist. The ultimate status of picrotoxin in comparison with better known analeptic agents, such as caffeine, strychnine, ephedrine, carbon dioxide and metrazol, remains to be determined. Like strychnine, it must not be employed in the treatment of morphine poisoning.

Curariform Drugs in Certain Neuromuscular Syndromes. Passing from central nervous system stimulants to skeletal muscular depressants, some mention may be made of curare, which in recent months has received considerable attention in the lay as well as the medical press. Curare and certain other alkaloids such as erythroidine, are capable of depressing neuromuscular junctions of skeletal muscles so that the response to nerve impulses is diminished or abolished. Older sporadic attempts to use curare clinically met with little success, due chiefly to difficulty in obtaining purified and standardized preparations. Lately, however, curare has been employed for the prevention of traumatic fractures incident to the metrazol therapy of schizophrenia. This has reawakened interest in the use of curare for other syndromes, and some measure of success has been obtained in patients with spastic paralysis, dystonia musculorum deformans, and torticollis. It is to be hoped that the active investigations now under way in a number of laboratories and clinics will provide curare-like preparations suitable for clinical use, and possessing a selective action on abnormally functioning muscles, as well as a wide margin of safety regarding respiratory and cardiovascular depression.

Oral Administration of Mercurial Diuretics. The successful use of organic mercurial diuretics by the rectal route allowed the hope that it would eventually be possible to give these valuable agents by mouth in patients with edema or ascites due to heart failure or cirrhosis of the liver. That hope stands on the threshold of realization and within the last year successful results have been obtained with a preparation of salyrgan combined with theophylline. Satisfactory diuresis results in approximately 70 per cent of patients. Although this figure is below

the 95 per cent success achieved by the intravenous route, it is higher than the 60 per cent obtainable by the use of mercurin suppositories. Untoward gastrointestinal symptoms such as epigastric discomfort and diarrhea are mild and infrequent. In patients who are not acutely ill and do not require immediate and drastic diuresis, the oral preparation may well prove to be the agent of choice and to have a definite advantage over the rectal route. At present, the drug is released only for investigational purposes, but if the success to date continues to be confirmed, it may soon be routine to administer mercurial diuretics by mouth. In employing either the oral or rectal route, the major contraindication to the use of mercury must still be rigidly observed, namely, that mercury is not to be employed if renal function is noticeably impaired. This holds true regardless of the cause of the edema.

Short-Term Massive Arsenotherapy of Early Syphilis. Being residents of the New York area, most of you undoubtedly are fully aware of the highly important work being done with the massive short-term arsenotherapy of early syphilis. This therapy holds great promise, and the public health and economic advantages are evident to all. Immediate clinical and serologic results are quite favorable, but several more years of intensive study will be required before the late clinical results can be determined and compared with those obtainable by the accepted routine of prolonged continuous therapy, as sponsored by the Cooperative Clinical Group. Much remains to be learned concerning optimal dosage, the arsenicals of choice, the duration of therapy, and the exact incidence of toxic reactions. It must be emphasized that the treatment is still relatively new and should be conducted mainly in those medical centers where adequate facilities for careful study are available. Only harm can come from promiscuous use of the method. It should be confined to patients with *early syphilis* and is strictly a hospital procedure. Deviations from the outline of treatment as described by the originators of the continuous intravenous drip arsenotherapy should be undertaken only by experts.

Sobisminol in the Oral Therapy of Syphilis. The status of bismuth as an adjuvant in the therapy of both early and late syphilis is well known. To the patient, however, an unpleasant feature of conventional treatment with bismuth is the necessity of intramuscular injection of the metal. Lately, it has been demonstrated that certain salts of bismuth in special solvents are adequately absorbed after oral administration

and exert chemotherapeutic effects in the tissues. Although this work is still in the investigational stage, the reports to date are promising. The preparation accepted by the Council on Pharmacy and Chemistry for oral use is *sobisminol mass*. Until more is learned concerning the action of sobisminol mass in syphilis, its employment should probably be restricted to patients unable to receive intramuscular therapy, and to supplant treatment by that route in patients compelled for a time to be out of contact with their physicians. Special limitations and dangers accompany the use of bismuth by the oral route, and these should be understood before employing it.

Rotenone as a Contact Insecticide. Rotenone is a drug recently introduced in clinical therapeutics after a successful career as a contact insecticide in agriculture and veterinary medicine. It has received much prominence in magazine articles and its collection, importation and use in the United States represent a growing and important industry. Obtained from derris root and at present from the South American cubé root, rotenone is a highly complex organic compound which is very toxic for insect pests but relatively harmless to warm-blooded animals. Its chief value in therapeutics is for scabies and for chigger-mite dermatitis. It is applied in the form of a one or two per cent lotion. Rotenone treatment is apparently effective and has the definite advantages over the usual scabeticides in not being odorous or messy, or causing staining or skin irritation.

Benzyl Benzoate as a Scabeticide. While on the subject of scabeticides, a word should be said about benzyl benzoate, a drug which had a short clinical trial about 15 years ago as an antispasmodic, a property which it fails to exhibit clinically. Benzyl benzoate now turns out to be an efficient scabeticide, and has been shown by the British to be effective after a *single* application. It has been found especially useful when people are living under air raid conditions and the danger of infection is great. Benzyl benzoate is applied as a lotion, which can be made with equal parts of the drug, soft soap, and alcohol.

Phenothiazine in Enterobiasis. Phenothiazine is another contact insecticide employed in agriculture as a lead and arsenic substitute with low toxicity for mammals. It was quickly found to be an excellent vermifuge for cattle, swine, sheep and horses. The urine of animals given phenothiazine was observed to turn red on exposure and not to putrefy. Investigation showed that phenothiazine — the mother substance of

methylene blue and certain other dyes—is excreted in the urine and eventually oxidized to thionol, a red antiseptic dye, especially if the urine is acid. This led to the clinical trial of phenothiazine as a urinary antiseptic. Although the drug showed considerable promise, mandelic acid was already firmly entrenched as a urinary antiseptic, and the sulfonamides were rapidly rising to first place. Not to be deterred, phenothiazine moved on to new fields and has within the last year been shown to be a very effective agent in the treatment of pinworms. Although enterobiasis hitherto has been particularly difficult to treat in children, it appears that a single five-day course of phenothiazine will cure 90 per cent of cases, and untoward symptoms are not experienced.

Gentian Violet as an Anthelmintic. Gentian violet, an antiseptic dye, is not a new drug but recently it has been put to new uses. It too has been found quite effective in the treatment of pinworm infestation. Like phenothiazine, it cures 90 per cent of cases after a single 10-day course of treatment. Unlike phenothiazine, however, gentian violet causes mild untoward gastrointestinal effects in a considerable number of persons receiving it. Gentian violet has also been found of value in the treatment of strongyloidiasis.

Atabrine in Giardiasis. Before leaving the subject of human parasitic infestations, mention should be made of the fact that atabrine, an effective synthetic antimalarial drug, has within the last year been established as a curative agent for giardial infestation in man. The dose employed is similar to that used in malaria, and cure is effected in nearly 100 per cent of patients. It is now possible to determine whether giardial infestation produces symptoms, because the organism is usually considered to be nonpathogenic for humans. Nevertheless, a large number of patients harboring the parasite complain of diarrhea, abdominal pain, asthenia and irritability. Evidence exists that a significant number of such patients may be freed of their symptoms by treatment with atabrine. Further work may indeed establish that the flagellate is mildly pathogenic. In any event, atabrine would appear to be a specific cure.

Intravenous Administration of Plasma and Tissue Protein Precursors. An extremely important field of research which may soon have direct clinical applicability concerns the parenteral administration of precursors of tissue and plasma proteins. The possibility of administering protein or its precursors by routes other than the oral has long engaged the imagination of medical investigators. Such therapy would prove

valuable in the treatment of a variety of conditions including hypoproteinemia, certain types of malnutrition, and dysfunctions of the enteric tract due to disease or surgery, characterized by inability to take sufficient protein by mouth. It has already been possible to inject amino-acid mixtures or protein digests intravenously in humans without appreciable toxic effects. Further advance in this important field awaits development of the proper types of commercial preparations—minimal criteria being lack of toxicity, reasonable price, and ability to meet the nitrogen requirements of the body. It is perhaps well to emphasize that this type of therapy is not suitable for shock, in which condition better and more rapidly acting therapeutic agents are available.

Synthetic Morphine Substitutes. The general practitioner is probably unaware that from 1929 to 1941, an extensive coöperative research program was in progress to study morphine, its derivatives, and substitutes, under the joint auspices of the National Research Council, The Narcotic Bureau of the United States Public Health Service, and the Universities of Virginia and Michigan. Many valuable contributions emerged from this extensive investigation. Of the many substitutes for morphine which were synthesized and studied, the one most promising is known as "metopon." Chemically, it is a methyl derivative of dilaudid. It appears to have definite advantages over morphine in that respiratory depression and emetic properties are less noticeable, and analgesic potency is more prominent than euphoria or narcosis. It also seems that metopon may have less liability for producing addiction. In other words, metopon offers greater analgesic power with less risk of addiction and with fewer untoward side-actions. Further clinical experience, however, is required to substantiate these findings. At present the drug is available only for investigational purposes.

Gramicidin in Bacterial Infections. The discovery of sulfonamides undoubtedly provided a sharp impetus to chemotherapeutic research in general, and particularly with regard to antibacterial agents. The good earth which yields our sustenance contains a wealth of important bacteria capable of performing many remarkable biochemical reactions. In 1939, from an aerobic sporulating soil bacillus, Dubos and associates isolated a bactericidal crystalline principle which selectively kills Gram-positive cocci, and which was therefore named gramicidin. Gramicidin is a crystalline substance, soluble in alcohol and acetone but not in water, and containing a number of amino-acids combined to form a

polypeptide. In the test tube, as little as 0.005 mgm. of gramicidin kills one billion pneumococci or group A hemolytic streptococci. The meningococcus and gonococcus are moderately affected, but Gram-negative bacilli are not susceptible. In mice, for example, a single intraperitoneal injection of 0.001 mgm. of the drug protects against 10,000 minimal lethal doses of pneumococci or streptococci, and larger doses cure well-established infections. Preparations of gramicidin at present available are not only water-insoluble but are also hemolytic. This restricts their clinical use to local application to the body surface and to irrigation of closed cavities. However, there is good reason to believe that water-soluble and non-hemolytic fractions of the drug may soon be available. Gramicidin has shown considerable promise in preliminary clinical trials in a variety of infections caused by Gram-positive cocci. Among the conditions successfully treated are the following: infected stasis ulcers, acute maxillary sinusitis, eczematoid dermatitis, wound infections, persistent cystitis, and pneumococcal empyema. No evidence of systemic toxicity has been reported as yet, tissues are apparently undamaged and healing of wounds is accelerated. Many problems concerning gramicidin are being actively studied and its eventual status, especially in comparison with local sulfonamide therapy, remains to be determined. The outlook, however, is very promising. At present, gramicidin is available only for investigational purposes.

Penicillin in Bacterial Infections. Another potent bactericidal agent obtained from cultures of microbial cells is penicillin, discovered in 1929 by Fleming, but developed to the point of clinical applicability only within the last year. Penicillin is so named because it is produced by a mould, probably *Penicillium notatum*, a first cousin to the mould responsible for the ripening of Camembert cheese. It is extracted from the culture medium, dried by the lyophilic method, and consists of a yellow, water-soluble powder, the chemical composition of which is not yet determined. Penicillin is active against a variety of microorganisms in dilutions of one to a million or more, including the streptococcus, staphylococcus, gonococcus, meningococcus, and anaerobes of the gas gangrene group. For example, in the test tube, 0.001 mgm. in one cubic centimeter of culture medium will inhibit the growth of 2,500,000 hemolytic streptococci. Most of the Gram-negative bacilli, however, are unaffected except by high concentrations. Experimentally, animals are protected by penicillin against numerous bacterial infections, and

mice can be prevented from succumbing to 100,000,000 lethal doses of streptococci. Penicillin differs from sulfonamide drugs in three important ways: First, it is more potent. Secondly, it completely inhibits bacterial growth even when the cultures are heavily inoculated, and this is of great importance in the therapy of heavily infected wounds. Lastly, penicillin is not inhibited by tissue autolysates, an advantage in the therapy of suppurating wounds. Being water-soluble, it can be administered to patients by a variety of routes, including the intravenous. Although clinical studies are as yet meager, those conducted by the group in Oxford, England are particularly encouraging. The drug has been employed successfully in patients with a variety of bacterial infections, including osteomyelitis, urinary tract infections, large carbuncles, infectious conjunctivitis, etc. It has proved valuable in cases which failed to respond to surgery or sulfonamides. Toxic effects have not been observed. At present, the chief handicap is the inadequate supply of the drug. The available evidence suggests that penicillin is an effective and potent chemotherapeutic agent of low toxicity, but its ultimate status in relation to gramicidin and sulfonamides remains to be determined.

Synthetic Estrogens (Diethylstilbestrol). In recent years, much experimental and clinical work has been done with synthetic estrogens. These differ from naturally occurring estrogens in that they are derived from a chemical known as diphenylethylene or stilbene. The most active member has therefore been named stilbestrol (diethylstilbestrol) because of its high estrogenic potency. The actions of diethylstilbestrol are almost identical with those of the naturally occurring estrogens, but the compound is many times more potent than estrone when administered orally, and from two to four times more active when given parenterally. However, after parenteral administration, it is less active than estradiol. The therapeutic indications for diethylstilbestrol are the same as for the naturally occurring estrogens, and the drug has been successfully employed in the treatment of many of the conditions requiring estrogenic therapy, such as menopausal symptoms, senile vaginitis, gonococcal vulvovaginitis, etc. The two outstanding advantages of diethylstilbestrol are first, that it can be given conveniently by mouth, and secondly, that it is much cheaper than other estrogens. However, there is some evidence that its use results in a fairly high incidence of mild toxic reactions, especially nausea and vomiting. Although not all

investigators have noted a significant incidence of untoward reactions and while it seems likely that these are mainly due to overdosage, nevertheless more information must be obtained to demonstrate that diethylstilbestrol is relatively non-toxic, and this factor should be weighed against those of cost and ease of administration in determining the choice of estrogenic preparation.

Progesterone Therapy in Threatened or Habitual Abortion, Functional Bleeding, Dysmenorrhea, etc. Although the active principle of the corpus luteum was isolated and chemically identified in 1934, the synthetic commercial preparation has been available for general use only within recent years. Sufficient clinical data have now accumulated to indicate the worth of progesterone therapy, but it must be emphasized that such therapy is relatively new and still in the stage of clinical experimentation. Progesterone has been employed successfully in threatened abortion. However, threatened abortion may be due to a defective embryo, and the administration of progesterone may then defeat nature's purpose in expelling the abnormal embryo. The drug has also been used in certain cases of habitual abortion. The mechanism of action of progesterone in maintaining pregnancy is apparently the suppression of uterine motility and, in the earlier stages of gestation, the maintenance of a proper type of endometrium to insure an adequate circulation to the fetus. The hormone may also logically be tried in certain cases of continuous functional uterine bleeding. The cause of the bleeding may be due either to endometrial hyperplasia associated with a progesterone deficiency or to hyperestrinism. In either case, progesterone therapy may be beneficial, but this should not obscure the fact that such a syndrome is based on an ovarian dysfunction. The cause of the dysfunction, often hypothyroidism, should be determined if possible. Reports of success with progesterone in some cases of dysmenorrhea are probably based on the fact that the hormone diminishes uterine motility. The same mechanism is concerned in the use of progesterone for afterpains following parturition.

GROUP III

In Group III are included those newer therapies which, in the opinion of the reviewer, are of questionable value and require much further investigation to delineate their proper status (Table III). Because of the controversial nature of the subject matter and the limitation of

TABLE III
RECENT THERAPIES OF QUESTIONABLE VALUE

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| Histamine (in allergic diseases) |
| Adrenal cortical hormones (in therapy and prevention of shock) |
| Renal anti-pressor extracts and tyrosinase (in essential hypertension) |
| Convulsive or shock therapy of schizophrenia (metrazol, insulin, nitrogen, etc.) |

time, only the briefest mention can be made of the topics in this category.

Histamine Therapy in Allergic Disorders. The indiscriminate use of histamine in a heterogeneous group of allergic diseases is certain to lead to disappointing results and to prevent a clear appraisal of the true worth of histamine desensitization therapy. While there is some evidence that histamine may be the causative agent of anaphylactoid symptoms produced by cold, its role in the etiology of other than physical forms of allergy is far from clear. The use of the amine in desensitization therapy must be considered for the present to be a procedure the value of which is far from established.

Adrenal Cortical Hormones in the Prevention and Treatment of Shock. The clinical use of desoxycorticosterone or other adrenal cortical hormones for the prophylaxis and treatment of shock is still a questionable procedure. Undoubtedly the employment of the hormone with large amounts of sodium chloride solution serves to increase the circulating blood volume by retention of salt and fluid. It is not clear, however, how such therapy could prevent the *onset* of shock, considering the pathological physiology of the syndrome. Also, there is real danger of overtaxing the circulation. The objective in treating shock is to increase the blood volume. Desoxycorticosterone does this by a renal mechanism. Shock is usually associated with anuria and the problem is not the loss of circulating fluid through the kidney but rather through widely dilated or injured capillaries. Until it has been more definitely shown that the adrenal cortical hormones influence the distribution of body fluids by affecting the permeability of capillaries, their use in shock must be viewed with a good measure of skepticism. Certainly, the clinical evidence is as yet too meager to warrant any definite conclusions as to the ultimate value of such therapy. Furthermore, a similar view must be adopted toward any other disease or symptom in which

the hormone is alleged to bring relief by a local corrective action on an increased permeability of capillaries.

Renal Extracts and Tyrosinase in the Therapy of Essential Hypertension. The technic of renal ischemia devised by Goldblatt for producing experimental hypertension in animals initiated an extremely important field of research which has profound implications for pathology and medicine. Not the least of these is the necessity for carefully re-examining all patients diagnosed as having essential hypertension with a view of ascertaining whether occult renal pathology is possibly responsible for the high blood pressure. Several investigators have attempted to isolate the vasopressor substance produced by renal ischemia, and extracts of kidney with antipressor properties have been prepared which are capable of preventing or reducing experimental hypertension in animals. Likewise, the enzyme tyrosinase, which is found in fruits and vegetables and especially in mushrooms, and which is capable of inactivating pressor amines such as tyramine and epinephrine, has been found capable of inactivating renin and angiotonin. This enzyme has also been found capable of lowering the blood pressure in experimentally produced hypertension in rats and dogs. Both tyrosinase and antipressor renal extracts of various sorts have been tried clinically and have been shown to be capable of lowering blood pressure in patients with essential hypertension. Despite the reported manometric success, this field of clinical investigation is altogether too new for one even to hazard a guess at the results which may ultimately develop. The capable workers engaged in this research would be the last to object to seeing their attempts at therapy of essential hypertension classified as questionable until much more clinical evidence is available.

Convulsive or Shock Therapy of Schizophrenia. With regard to the convulsive or shock therapy of schizophrenia, whether induced by drugs such as metrazol or insulin, or by other means such as nitrogen, it is the opinion of the reviewer, from an examination of the available evidence, that such treatment has questionable and certainly limited value, and is not without serious danger. Clearly, the procedure should be restricted to institutions where the staff is adequately trained in this highly specialized technique. The mechanism of action is not clear, and whether the alleged favorable results are due to temporarily reduced cerebral oxidations or to actual cortical damage is not known. So many "cures" of schizophrenia have been endorsed enthusiastically only to be

TABLE IV
RECENT THERAPIES OF LITTLE OR NO VALUE

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| Pyridoxine (in parkinsonism, amyotrophic lateral sclerosis, muscular dystrophies) |
| Alpha-tocopherol (in amyotrophic lateral sclerosis, muscular dystrophies, habitual abortion) |
| Testosterone (in "male climacteric," prostatic hypertrophy, etc.) |
| Histaminase (in allergic diseases) |
| Potassium salts (in allergic diseases) |
| Bulgarian belladonna (in parkinsonism) |

discarded after long-term study that one can hardly be criticized for adopting a cautious view with regard to convulsive or shock therapy. This cautious view necessitates that such therapy be classified for the present as questionable and requiring much further study before its ultimate worth can be ascertained.

GROUP IV

In Group IV are placed those newer drug therapies which, in the opinion of the reviewer, are either extremely questionable in value, or irrational and destined for eventual discard (Table IV).

Pyridoxine in the Therapy of Parkinsonism, Amyotrophic Lateral Sclerosis and Muscular Dystrophies. Pyridoxine, or vitamin B₆, is a recently discovered component of the vitamin B complex. Although essential in animal nutrition, its significance in human nutrition is not yet known. Therefore, pyridoxine has no clear-cut therapeutic indications, and until such time as specific deficiencies are attributable to its lack it cannot be considered an indispensable drug. This does not mean that the active research now being conducted will not soon yield results translatable into daily practice; but, it does explain why disease entities not specifically due to a lack of pyridoxine cannot reasonably be expected to respond to pyridoxine therapy. Thus, the early sanguine reports of success with pyridoxine in treating such varied syndromes as parkinsonism, amyotrophic lateral sclerosis, and muscular dystrophies have not been confirmed by carefully controlled clinical experiments. One may safely venture the prediction that when pyridoxine is ultimately established as a valid therapeutic agent, it will be for treatment of diseases or symptoms specifically due to a lack of the vitamin.

Alpha-Tocopherol in the Therapy of Amyotrophic Lateral Sclerosis

rosis, Muscular Dystrophies, and Habitual Abortion. Alpha-tocopherol, or vitamin E, is not a new vitamin, but it has only recently been synthesized. Although it is apparently necessary in the nutrition of certain but not all species of animals, its significance in human nutrition is unknown. Because growth, normal pregnancy and prevention of muscular dystrophies in rats require alpha-tocopherol in the diet, the drug was quickly tried in humans with disturbances only superficially resembling the deficiency states observed in animals, and with results that one might easily anticipate, namely, not very encouraging. Thus the early enthusiastic reports concerning the use of alpha-tocopherol in amyotrophic lateral sclerosis, pseudo-hypertrophic muscular dystrophy, and habitual abortion were destined to be challenged and denied by later more carefully controlled clinical experiments and observations. As in the case of pyridoxine, indeed, as in the case of all vitamin principles, one may safely predict that when the clear-cut indications for alpha-tocopherol are finally disclosed, they will certainly relate to deficiency states proven to be specifically due to a lack of the vitamin.

Testosterone in the Therapy of "Male Climacteric," Prostatic Hypertrophy, etc. Testosterone has been employed clinically only within recent years. Although experience with it is therefore limited, evidence is available concerning its unquestionable value in both prepuberal and postpuberal castrates. Indeed this use appears to be the main field of valid therapy with testosterone. Unfortunately, older concepts concerning the male sex hormones are influencing modern therapy, and one can detect a trend toward emphasis on the ability of androgens to restore sexual activity. Advertising brochures thus recommend their use in such vaguely defined conditions as the "male climacteric" and "atonicity." Such exploitation can do much harm. Also, on rather incomplete evidence, testosterone has been employed for prostatic hypertrophy, but there is little reason to believe that androgen therapy can cause the involution of an existing hypertrophy. Indeed, there is always the possibility that it may cause a still greater enlargement of the gland. Furthermore, testosterone has been employed for relief of a wide variety of conditions, including dysmenorrhea, menopausal states, peripheral vascular disease, painful breasts, menorrhagias, and for interruption of lactation. Much more evidence is required before one can say whether such therapy is rational or safe. It is indeed unfortunate that as soon as an endocrine principle or vitamin is isolated in pure form, synthe-

sized and placed in ampules, it is used indiscriminately in a variety of unrelated diseases, and an avalanche of uncritical case reports is soon loosed upon the medical profession. It often takes years to unearth the truth from this avalanche. A clear understanding of the basic physiology involved should greatly assist one properly to select those clinical conditions in which there is an adequate rationale for specific hormone therapy.

Histaminase in the Therapy of Allergic Disorders. Histaminase is an enzyme which, under special test-tube conditions, can inactivate histamine. It has been widely employed in a large heterogeneous group of allergic conditions. As with all new therapies, some enthusiastic initial reports are bound to appear, but slowly the long-term and more deliberate studies serve to nullify or reverse the original over-enthusiastic appraisal. In the opinion of the reviewer, those most qualified to pass judgment on histaminase therapy have adequately proven not only its unsound theoretical rationale, but also its clinical inefficiency. The physiological background concerning the enzyme and the role of histamine in allergy are both so poorly understood, it is little wonder that the clinical use of the enzyme is disappointing. To those who claim that they have occasionally obtained excellent results with histaminase, one can only reply by reminding them of the vagaries and perversity of biological subject matter.

Potassium Salts in the Therapy of Allergic Disorders. What has been said with respect to histaminase in the therapy of allergic conditions holds true for potassium salts even to a greater extent, if that is possible. While salts of potassium are useful in promoting diuresis, in preventing or curing attacks in patients with familial periodic paralysis, and in the diagnosis of Addison's disease, it remains to be demonstrated that they are of any benefit whatsoever in the treatment of diseases of allergy. The theoretical basis for the employment of potassium salts is nebulous and the extravagant claims made for such therapy are fully disproved by the results of carefully controlled clinical studies. Indeed, how can one expect to obtain dramatic relief from allergic symptoms by the administration of a daily dose of potassium which represents but a small fraction of the normal daily dietary intake of this ubiquitously distributed cation?

Bulgarian Belladonna in the Treatment of Parkinsonism. As you probably know, Bulgarian belladonna root has recently enjoyed some

popularity in the symptomatic treatment of patients with parkinsonism, and exaggerated claims have been made for its virtues. One can summarize the best information available on this question by stating flatly that Bulgarian belladonna root has no special advantages over belladonna root grown in the United States. However, as a result of the unfounded claims made for Bulgarian belladonna root, there has resulted a re-examination of the use of alkaloidal mixtures in parkinsonism. Studies now in progress may eventually show that U.S.P. Belladonna Root is superior to official belladonna leaf, at least in some patients. It also may eventually prove to be true that white wine extracts occasionally give better results than tinctures. Finally, there is some evidence that certain individuals respond more satisfactorily to mixtures of purified alkaloids than to any single alkaloid employed alone. These points, however, remain to be determined. What is certain is the fact that one may safely continue to patronize home-grown belladonna.

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A NOTE ON WAR PSYCHIATRY*

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At the time of our joining our allies in the first World War, American Psychiatry had the advantage of scrutinizing the experiences of the other combatant nations on both sides of the struggle with respect to the psychiatric issues involved. Our attention was challenged by two important facts which were reflected in the published accounts of the medical authorities of the nations at war: First, the substantially greater prevalence of psychiatric casualties among soldiers than among the civilian population, and second, the emergence of new and hitherto unobserved disorders of function which were in a general way referable to the nervous system.

With respect to the first observation, namely, the markedly increased incidence of psychiatric casualties among troops, it was observed that not only in actual war but even during peaceful mobilization, such as that of our army along the Mexican border in 1916, there was a higher rate of mental disease among soldiers than in civil life. The discharge rate for mental diseases in the United States Army in 1916 was three times the admission rate for these disorders in the adult male population of the State of New York, one-tenth of all discharges for disability being for mental diseases, mental deficiency, epilepsy and the neuroses.

It was largely through the efforts of the late Thomas W. Salmon that the significance of these observations was brought to the attention of the medical authorities of the War Department, which up to then had shown relatively little concern in psychiatric issues. As a result largely of Salmon's efforts, the coöperation of the Army Medical authorities was gained for putting into practice the recommendations outlined by a group of psychiatrists and neurologists under Salmon's leadership. It was my privilege to participate in the early deliberations on these matters and I wish to take the opportunity here of attesting to the rare wisdom, courage and high qualities of leadership which Salmon displayed during

* Read at the annual meeting of the New York Society for Psychotherapy and Psychopathology at The New York Academy of Medicine.

these deliberations. It would serve no particular purpose to give a detailed account here of the clinical and administrative techniques which were finally adopted, although I shall go into greater detail later on with respect to the clinical aspects of the subject.

At the time of the creation of the Division of Neurology and Psychiatry in the Surgeon General's office, about fifty neuropsychiatric officers had been commissioned. Five months later there were two hundred and thirty-five, and at the time the armistice was signed there were 430 officers in this country and 263 overseas, a total of 693. I mention these figures in order to indicate the drain which the requirements of the Selective Service Administration will mean to civilian psychiatry. These officers were assigned in a general way to two types of duty: First, the routine neuropsychiatric examination of recruits, and second, clinical and administrative service in base and other military hospitals.

It was impossible to determine with absolute accuracy how many men were examined by the neuropsychiatrists in this country, but the figure finally adopted for statistical considerations was 3,500,000. Of this number there was a total of 69,394 psychiatric diagnoses, and of these 533 referred to officers and 587 to candidates for commission.

These psychiatric diagnoses comprised the following entities: 31.5 per cent mental deficiency; 16.5 per cent psychoneuroses; 11.4 per cent psychoses; 10 per cent nervous diseases and injuries; 9.2 per cent epilepsy; 8.9 per cent constitutional psychopathic states; 6.9 per cent endocrinopathies; 2.9 per cent drug addiction; 2.7 per cent alcoholism.

Thus 20 out of every 1000 examined had some form of mental or nervous disease or defect.

According to the British official history of the Great War, the psychiatric problem in the British Expeditionary Forces did not become acute until July 1916, when several thousand patients were rapidly passed out of the Somme battle zone. An analysis of 1,043,653 British casualties revealed that neuroses formed 34 per 1000 casualties. On occasions neuroses made up 40 per cent of the casualties evacuated home. In 1918 out of a total 160,000 pensioners, 32,000, or 20 per cent, were receiving pensions for functional nervous and mental disease, while in 1921 this figure had risen to 65,000. Of the 180,496 casualties which occurred in the Canadian Expeditionary Force, 24 per 1000 were included in the category of nervous and mental disease.

According to various authors, the incidence of psychiatric casualties

was relatively greater in fresh troops arriving in the front line; in battle-tested troops after prolonged trench life without a break; in men over 40, especially married men, and in rapidly trained volunteers as compared with the regular army. The incidence rose considerably after severe military operations, actively advancing troops were less liable to breakdown than inactive or retreating troops, technicians working at the front under extreme hazard, infantry and machine gunners, engineers, artillery and tank corps ranked high on the list.

It is interesting to compare the above ratios of casualties in the B. E. F. and C. E. F., 34 to 40 per thousand in the former and 24 per 1000 in the latter with the ratio of casualties in the A. E. F., where during the period between April 1917 and December 1919 it was 9.5 per 1000. One reason for this markedly lower incidence of psychiatric casualties among the A. E. F. that is frequently given, especially by foreign authorities, is the comparatively short period of active service that our forces had abroad. While this factor cannot be ignored, I would like to stress especially in this connection two other factors which account for this important difference in the ratio of casualties. The first is the really competent job which the neuropsychiatrists did in weeding out the incompetents on this side of the ocean. It is significant in this connection that 27,836 cases or 40.1 per cent of the total of 69,394 were detected and certified as unfit in the course of the routine neuropsychiatric examinations. Other sources of spotting the unfit were as follows: 31.6 per cent came to light as result of psychiatric consultations requested by other medical officers; 23.6 per cent were referred by commanding officers, non-medical. In connection with this truly significant item, namely that 16,336 cases of psychiatric abnormalities were detected by line officers, I would like to stress the great importance of a deliberate and well organized technique for educating non-commissioned as well as commissioned officers to observe and recognize abnormalities of conduct which was carried out by the American neuropsychiatrists as part of their routine duties. This is one feature of the psychiatric experiences of the first World War, which might well be immediately instituted in connection with our present mobilization tasks. 1.3 per cent of the cases were referred by the psychologists, a rather inexplicable phenomenon in view of the fact that the psychologists had a fine opportunity for observing the soldier in connection with the administration of the intelligence tests; 0.3 per cent were disciplinary cases, and in 3.1 per cent of

the cases the source of detection of the abnormalities was not ascertained.

The second important factor which undoubtedly contributed to the marked lessening of the incidence of neuropsychiatric casualties among the A. E. F. was the manner in which these casualties were managed and treated when they occurred. Before discussing this point, let me again stress the significant prophylactic work which the original elimination technique accomplished. This fact was recognized by a number of American as well as European authorities. After some little experience the average psychiatrist could rapidly survey between 100 and 150 recruits a day with reasonable accuracy. Close and trained observation and a brief but pointed conversation in connection with the physical examination enabled us to detect those who required a more detailed examination. Curiously, but perhaps not so strangely after all, the main difficulties with regard to action on the psychiatrist's recommendation were encountered at the hands of the general medical officers of the disability boards, whereas the line officers who rated their men in terms of conduct, behavior and efficiency, were extremely sympathetic and coöperative.

I dwell upon this prophylactic side of the problem because it is also the most urgent and the most important problem confronting us today in connection with our mobilization. It should be remembered that those accepted into the army in connection with the Selective Service Law are not only obliged to live under military conditions for one year but remain in the army reserve for 10 years thereafter. Apart from the personal suffering of those who might have escaped a breakdown under civil life, had their predisposition to breakdown been recognized, failure to do so creates an incredible economic burden. Of the 68,727 post-war cases under hospital care by the Veterans Administration in June 1940—twenty-two years after the termination of the first World War—20 per cent were neuropsychiatric patients.

Up to the present over one billion dollars have been expended for the care of and for the various benefits granted to these neuropsychiatric patients.

The administrative procedures which are being followed in connection with the present Selective Service Law, will undoubtedly assist the draft boards in detecting a certain number of draftees who are unfit for army life. But we must not deceive ourselves concerning the limitations and shortcomings of such a necessarily rapid and superficial survey. To

be sure, these boards will have before them a great many personal data which the draftee is obliged to supply, a careful scrutiny of which might furnish a hint which should put the examiner on guard. But I think it might help matters if the authorities charged with this important aspect of the work would carefully scrutinize the literature for technical hints in clinical situations similar to those which confront the draft boards. We all recognize the importance of time and coöperation in arriving at a psychiatric diagnosis apart from clinical technique. Permit me to refer to two situations in my own experience which in some ways are not very much unlike the situation confronting the draft boards.

Many years ago, I was engaged in the neuropsychiatric examination of immigrants at Ellis Island. In a paper published following that experience, I pointed out, among other things, that usually we had less than one minute for the preliminary scrutiny of an immigrant, as these people passed before us in single file. It was remarkable how often minor, and what appeared to be insignificant characteristics in posture, gait, general attitude and response to a question or two were sufficient to lead us to select an immigrant for a further examination, which proved to be justified in a remarkably large number of instances.

An effort was made by several of my fellow officers who shared with me the experiences at Ellis Island to examine critically what it was in the nature of hunches or techniques which assisted us in carrying out this difficult job of rapid-fire detection of neurological and psychiatric difficulties. It is estimated that the Medical Advisory Boards of the Selective Service Administration will have about 15 minutes for the secondary, and I think final examination of those suspected of having psychiatric disabilities. It would be well for them to scrutinize whatever literature there is with reference to our experiences in the examination of immigrants in those days when they were coming in at the rate of 100,000 a month at Ellis Island alone.

The other point I wish to touch upon is the importance of coöperation in arriving at a psychiatric diagnosis. Some twenty odd years ago I was engaged in the psychiatric examination of the prisoners at Sing Sing. One of the first difficulties we encountered there was the very prevalent attitude of suspiciousness on the part of the prisoners in connection with any attempt to inquire into what they called their strictly private affairs.

Besides, the benighted lot of prison guards of that day very quickly

dubbed me the "nut doctor" and very quickly succeeded in carrying over to the prisoners the idea that an interview with me meant all sorts of possibilities of further burdening their lot, and came to use it as a threat of punishment. I suppose the situation is very much different with respect to these matters today. But in those early days, when the psychiatric study of prisoners was still a novelty, we had to cope with many serious difficulties in gaining the necessary coöperation of the prisoners. We naturally tested all sorts of devices for overcoming these difficulties and one of these devices seemed to be of great assistance in giving us a hint, at any rate, as to what sort of personality we might be dealing with in a given case. As soon as the prisoner was admitted and practically while he was undergoing his preliminary ablutions, an intelligent, long term fellow prisoner, who assisted us in this work, gave the new inmate a sheet of paper and envelope and suggested that he write a letter to the doctor and address it to him in the sealed envelope. He also hinted that it was part of the prison routine, a little actual deviation from fact which the prison administration agreed to wink at. The letters we received were as a rule very revelatory, indeed, and constituted a very helpful point of departure in connection with the first interview. Especially revealing were those occasional epistles which consisted of just a blank sheet of paper and nothing else.

I am wondering whether, if time permitted, the carrying out of such additional steps in the work of the already overtaxed draft boards would not be a valuable aid in hinting at certain psychiatric difficulties which are somewhat obscure and difficult of detection. I am wondering whether it wouldn't be helpful to ask the draftee to accompany the formal questionnaire which he is asked to fill out by a private and sealed letter to the doctor on the draft board. Some things might come to light in this way which never would be revealed in the official and formal questionnaire. I am aware that in suggesting this rather unofficial and certainly, unmilitary deviation from the legal provisions of the Selective Service Law, I am not only exposing myself to the admonition that such informal and perhaps mitigating gesture might well be all right for civil life but has no place in military matters, but I'm also certain to run up against the ancient bugaboo of malingering. As far back as 1916 I published a somewhat detailed study of malingering and came to the following conclusions at that time.

1. The detection of malingering in a given case by no means excludes

the presence of actual mental disease. The two phenomena are not only not mutually exclusive, but are frequently concomitant manifestations in the same individual.

2. Malingering is a form of mental reaction manifested for the purpose of evading a particularly stressful situation in life, and is resorted to chiefly, if not exclusively, by the mentally abnormal, such as psychopaths, hysterics and the frankly insane.

3. Malingering and allied traits, viz: lying and deceit are not always consciously motivated modes of behavior, but are not infrequently determined by motives operative in the subconscious mental life, and accordingly affect to a marked extent the individual's responsibility for such behavior.

4. The differentiation of the malingered symptoms from the genuine ones is, as a rule, extremely difficult, and great caution is to be exercised in pronouncing a given individual a malingerer.

Such experience as I have had in the twenty-five years since then has confirmed me in the views expressed above. Apart from the fact that most authorities agree that the question of malingering played a very insignificant role in the psychiatric experiences of the last war, the resort to malingering on the part of the draftee, especially the malingering of a psychiatric difficulty, should in itself constitute a very strong presumption in favor of considering such an individual unfit for military service. As is so ably pointed out by Mr. Dykstra, the Director of the Selective Service Administration, in his preface to medical circular No. I: "Military life requires that the soldier shall be able to comfortably live in continued close contact with a variegated group of other men. He cannot depend on any self-evolved protective mechanism that sets him apart from his fellows. Military and naval experience is in favor of excluding from the armed forces all persons discovered to have mental or personality handicap of any material degree." Resort to malingering in an attempt to escape military service, should, in my opinion, constitute a sufficient cause for further careful psychiatric observation, if not for rejection forthwith.

It may be that I have devoted a disproportionate amount of the time allotted to me this evening to a stressing of the importance of detecting the mentally unfit draftee. But failure in this phase of psychiatric service is bound to create serious difficulties for the individual soldier as well as for the army. I am convinced, after re-reading the psychiatric

literature of the last war, that the most important contribution which psychiatry made was the prophylactic job of eliminating at the very beginning those who were unfit for military service. Many years ago, Kraepelin's Clinic at Munich issued the dictum that the mere fact of an individual's capacity to develop a psychogenic personality disorder was proof that he was burdened with what they termed a degenerative constitution. I questioned at that time the complete validity of that assertion and still question it today, though not so convincingly as in my youth. But I still doubt whether a predisposition to a failure to manage adequately the devastating experiences of modern warfare necessarily indicates a serious personality defect. The conflict between the forces which condition the desire to live and the avoidance of annihilation, on the one hand, and of those forces within the individual which are responsible for those highly complex attitudes of loyalty, patriotism and honorable behavior as a member of a group, on the other hand, may be unmanageable in the best of men. As a matter of fact, quite a few of the combatants, both officers and men, who subsequently suffered from manifestations of so-called "shell shock" had been decorated for an extraordinary display of bravery and capacity for sustained and unflinching effort under extremely harrowing situations. So that at best we cannot foresee a certain number of these casualties.

Earlier in this paper I stated that I attributed the substantially lower ratio of neuropsychiatric casualties in the A. E. F. as compared with the ratio of the B. E. F. not only to the much briefer participation of our forces in actual warfare but also to the prophylactic measures carried out in this country and to the manner of treating and managing the casualties in the A. E. F. as they occurred at the front.

Here again the country owes a great debt to the late Thomas A. Salmon. I shall briefly quote from the official history the general principles upon which the management and therapy of the neuropsychiatric casualties in the A. E. F. were based. These principles were evolved in consequence of the recommendations made by Salmon's Committee already referred to above. Stated broadly they were: "First, that it is not only in accordance with the best scientific practice to treat soldiers suffering with war neuroses as early and effectively as possible but to do so is an important contribution towards the conservation of man power and military morale; second, that a point of view regarding these disorders based upon a rational conception of their physiological and psy-

chological origin should at all times be maintained and should form the basis for medico-military effort; third, that in neuropsychiatric work, as far as the exigencies of actual service permit, responsibility and leadership should rest in the hands of those who had had special training in this department of medicine. The success attained was due, first, to a clear conception on the part of the highest military authorities of the objectives to be reached and of the general plan to be followed in attaining them, and second, to the cooperation of several hundred specialists in neuropsychiatric work in connection with combat troops, general and special hospitals, courts-martial, camps, classification boards, and prisons."

I shall leave the detailed discussion of therapy to a later section of this review. But in order to indicate by contrast how important the principles quoted above really were in keeping the casualties in the A. E. F. at a uniquely low level, I just want to mention that one way in which commentators classify the therapeutic approaches during the first World War, is to divide them into the authoritarian and the benevolent methods. During the early phases of the war, and indeed almost up to the time when the method employed in the A. E. F. became known, many psychiatric authorities, especially in the German armies, looked upon the war neuroses as akin to malingering; treatment was a matter of punishment and included such measures as isolation (solitary confinement), severe restriction of diet, transfer to excited psychotic wards, application of painful electrical currents, prolonged baths until recovery. A man named Kaufmann was the chief exponent of the most rigorous form of electrotherapy. His method consisted of three phases: (1) suggestive preparation; the patient was told that painful electrical currents would be applied which were certain to cure his condition; (2) application of strong faradic currents for one or two hours; (3) active military exercises. The cure was usually completed in one sitting. This method, originally received with great enthusiasm because of the rapid recoveries, was later generally discarded when fatal cases occurred, and permanency of results was doubted. The above is a good example of what was meant by the authoritarian approach.

The post-war generation of psychiatrists had the unique privilege and the very stimulating experience of living through a period in the history of psychiatry more exciting, more challenging and more pregnant with opportunity for service than at any time before. No one can

question the fact that the psychiatric experiences of the first World War had a great deal to do with this. But I fairly shrink from the task of compressing within the scope of a brief paper a detailed analysis of the factors which made for this cause and effect relationship.

For one thing, never before in the history of medicine had psychiatrists been called upon to deal with such incredibly large numbers of acute psychiatric casualties within such a relatively brief period of time. For another thing, owing to the almost universal presence among these casualties of at least one common etiological factor, namely, the war experience, our then-current and relatively new orientations concerning functional disorders had the first opportunity of being tested on a very large scale. While it is true that both in connection with the immediate call for doing something about these casualties as quickly as possible after their occurrence, as well as in connection with the final assessment of the total experience in the various medical histories of the first World War, various degrees of deviations, dissent and compromise with the then-valid psychoanalytic theories are clearly reflected, nevertheless, nothing emerged from this mass experience of humanity in the throes of anxiety and fear, to challenge successfully the fundamental tenets of Freudian psychology.

As a matter of fact, as soon as the medical officers, and the line officers too, realized the great therapeutic value of turning to the invalid himself for an explanation of his troubles, instead of labelling him on the basis of some preconceived general notions, the shift took place from an authoritarian to a benevolent management of war neuroses. It then also became impossible to fail to recognize, as the younger Miller puts it, that the central motive around which all the clinical manifestations seemed to collect, was the conflict between conscience on the one hand, and instinct on the other. You might substitute, if you wish, for the word conscience the word super-ego, and you might join those who are still engaged today in the fruitless enterprise of classifying and naming the instincts of man. But the essence of the matter is right here. It did not escape the notice of many army psychiatrists in both the A. E. F. and B. E. F. that the shell-shocked patient rarely suffered from an actual bodily injury; that on the contrary, the sustaining of an actual injury, which promised the reward of removal from the scene of war, actually eliminated the necessity for a neurosis. Leri's statement that hysteria never occurred in an open battle, was largely justified. They

recognized the great danger to recovery of a fixation of the initial symptoms, and implemented this by placing psychiatrists as near as possible to the front line.

Naturally, they recognized the importance of fatigue, exhaustion, the shock of nearby explosions and detonations, and the possibility of actual brain concussion; all of the factors contributing to a lessening of ego-resistance which weakened repression, disturbed the balance between the contending forces of the intrapsychic conflict and permitted the emergence of the neurotic symptoms.

The passing in review of such large numbers of war neuroses brought into sharp relief the difficulty of differentiating between the different types of disorders, since, as we know also from civilian experience, strict differentiation is much more possible when the disorder is in an advanced state. Nevertheless, it was considered to be of some therapeutic value to differentiate between the cases as sharply as was possible, and to attempt to discover outside of the great prevalence of common reactions those features which were especially characteristic of the individual invalid under treatment. At Base Hospital 117, which came to be the ideal prototype for base hospital psychiatric organization, research and therapy, the following classification was employed: Neurasthenia, psychasthenia, hypochondriasis, hysteria, anxiety neurosis, anticipation neurosis, effort syndrome, exhaustion, timorousness or state of anxiety, concussion, malingering.

It is hardly worth while to enter into a detailed consideration of the clinical manifestations which led to the above classification. The symptomatology was markedly affected by the time and place of its occurrence and by the immediate precipitating events.

Of more immediate interest is what the literature reflects regarding prognosis, in view of what world events might hold in store for us. Fundamentally, as far as prognosis is concerned, the war neuroses are subject to the same conditions which are operative in civil life. The literature reflects the opinion that prognosis is affected by the age and intelligence of the patient. Naturally, actual breakdowns or pronounced character difficulties before enlistment, and a preponderance of endogenous over exogenous factors, were of bad prognostic significance. This again focuses our attention upon the importance of weeding out the unfit before exposing them to the experiences of war. Furthermore, early treatment and the place where treatment was instituted definitely

affected the outcome, while premature discharge from treatment often led to a recurrence of symptoms. The anticipation of being discharged from treatment sometimes led to a reanimation of the disorder. If this reaction, indicative of a resistance to giving up the secondary gains of the illness, was ignored and the soldier was returned to his unit in spite of the new flare-up of symptoms, the symptoms usually became aggravated during the transport; when he finally rejoined his regiment, he was often in such a state that immediate readmission to a hospital was unavoidable. Thereafter, he occupied hospital beds for weeks or months, and relapsed after discharge. Now these types of reactions are familiar to us in civil practice and I need not dwell upon them in detail. But it is important to recognize that psychiatry could only compromise with the optimum requirements for adequate therapy in the service of military requirements up to a certain point. When these limits were exceeded failure was commonly the result.

War psychiatry, as you see, is an eminently and urgently practical affair. The requirement which was constantly urged upon the psychiatrists to restore the invalided to active duty as soon as possible and in as large numbers as possible frequently came in conflict with the therapeutic principles in the individual case. But it can be said that on the whole, as time went on, psychiatry was increasingly accorded its due recognition and gained for itself in increasing measure favorable working opportunities. Sixty-five per cent of those treated at the advanced clearing stations were returned to front line duty after a few days' treatment.

If what the future holds for us in this country includes the tragic necessity of another expeditionary force, psychiatry is bound to be infinitely better equipped than it was during our last tragic experience to deal with its problems. Of course, the conditions of warfare in 1941 and in the days ahead are very different than they were in the first World War, and unquestionably will bring with them new and untested problems.

For one thing, it is as yet impossible to assess accurately the effect of modern warfare upon the civil and non-combatant population. We are told that a certain widespread "numbness" to daily happenings is affecting large numbers of the English people. It may well be that we shall be obliged to apply to the civil population some of the lessons we learned in connection with the war effort. The techniques for producing

and maintaining the "war of nerves" have attained a high degree of perfection, and steps will undoubtedly have to be taken to insulate some people against the effects of it. For this reason it is very gratifying to know that the draft boards are exercising a very liberal attitude indeed, in the matter of weeding out the unfit. We are told that in England an increasing number of private employers are instituting morale-maintaining measures among their employees, as a defense against the effects of the "war of nerves." In all these measures, psychiatry will undoubtedly be called upon to play an outstanding role.

In conclusion I would urge upon you to read the January, 1941 issue of the *American Journal of Sociology*, and to re-read Freud's essay on *War and Death* and White's *Reflections on the War and After*. I recommend this, because it might help us individually to re-assess our personal equipment as men and women for its worth in meeting the tasks which will surely be thrust upon us in the days to come. We are committed as a nation to do everything in our power to resist and eventually eliminate the menace that comes to us from across the seas. One of the inescapable features of this task will be the growing necessity of converting our country into what has been termed a Garrison State, where the requirements of the military machine come before everything else, to say the least. At its worst, such a radical change from peacetime pursuits and peacetime freedoms and privileges will call for a readjustment of loyalties which the average man will surely find difficult of accomplishment.

FRIEDRICH AUGUST KEKULÉ

*Architect of Atoms**

HERMAN GOODMAN

I t has been said, with truth, of August Kekulé that he bridged the gap from alchemy to modern chemistry . . . Let us define alchemy.

Alchemy: The medieval chemical pseudoscience whose great objective was the transmutation of base metals into gold; the universal cure-agent for disease; the elixir of perpetual life.

Another definition found in books assumes alchemy to mean an infusion or mingling as juice or liquid, especially as extracted from plants for purpose of medicinal ingredients.

What was the world-wide state of alchemy on its road to chemistry in 1865? What was considered Chemistry? Glance at a text professing to be on the subject of chemistry at that period. You are struck at once with the absence of symbols. The shorthand scrawlings and scratchings by which thinking men transferred their thoughts were lacking, for the alchemy turned to chemistry.

Symbols for chemicals, and for chemical reactions, or, for that matter, symbols for structure, were absent—undiscovered, undefined. It was a long and devious travail. Many names are found again and again in a recital of the birth of modern symbols for chemical structure; Berzelius was one. His pupils included Wöhler who forged the chain between inorganic chemistry and organic chemistry. A name linked with that of Wöhler is von Liebig, father of Agricultural Chemistry. von Liebig had a pupil whose name was Friedrich August Kekulé.

Briefly, in a most elementary manner, we review the situation in chemistry at this period. Chemists could and did make analyses. They were able to determine the ingredients. They knew the types of elements. They could enumerate them. The plan of their union was lacking. The arrangement was missing. The blue print of organization was

* Read January 8, 1941 before the Section of Historical and Cultural Medicine of The New York Academy of Medicine.

not available. Linkage became most vital to advance. No one had told about linkage. No one had given a comprehensive and working plan which could withstand criticism. No one had done this: Kekulé found the answer to the riddle in a dream.

Friedrich August Kekulé was born in Darmstadt, September 7, 1829. He showed early talent in drawing and entered the University of Giessen with the intention of studying architecture. Through Liebig's lectures which he attended at Giessen, Kekulé was first attracted to chemistry. Family opposition to his desire to change from architecture to chemistry exiled him to Darmstadt where he managed to study some chemistry. In 1849 he was permitted to return to Giessen where he studied under Will and then again, Liebig. After a year, Liebig told him that he would probably ruin his health if he tried to become a good chemist. As a matter of fact, Kekulé for many years allowed only three or four hours each day for sleep.

In 1851 came an opportunity to go to Paris where Kekulé attended lectures. One day he saw a poster which announced that Charles Gerhardt, ex-professor of Montpellier, was offering lessons in chemistry. He entered his name for these classes. Gerhardt had seen Kekulé's name in Liebig's "Letters on Chemistry." He sent for the young student and offered him the post of assistant. Kekulé did not accept. He continued for a year to attend the lectures and gave much credit later to the inspirational visits he had with his teacher, Gerhardt. Giessen conferred on him the degree of Doctor of Philosophy, July 15, 1852. Then Kekulé went to Switzerland to work with Von Planta, and later to London as assistant to Stenhouse. Kekulé's first independent publication was printed in English and had to do with valence in organic compounds (1854).

During his stay in London, Kekulé was striving to answer the riddle of linkage. The time was about 1856. A glutton for work, and always in need of sleep, Kekulé sought his way by bus to his modest lodging in Clapham Road, after an evening of discussion with his friend, Hugo Müller, in Islington. Riding atop the bus, he fell asleep. He had a strange dream. Molecules gamboled with impish glee. For the first time Kekulé was enabled to discern the nature of molecular motion; to see clearly the precise method of molecular madness. He saw diminutive atoms frequently pair off and be embraced by larger atoms. He saw still larger atoms hold three or four small atoms, while the entire group kept

whirling about in a giddy dance, the large ones forming a chain. Awakened by the cry of the conductor, "Clapham Road," Kekulé spent the night transferring his reveries to paper. Out of this dream grew a system of constitutional formulas representing the structure of molecules of the open-chain type.

Kekulé was homesick in England. He wanted to teach in a German University. With this end in mind he returned to Germany and became a travelling student. In the winter of 1856 he became a dozent at Heidelberg. Here he did some of his most important work in a small private laboratory, a single room with an adjoining kitchen. He had a few pupils, among them Baeyer. It was in this little kitchen that Kekulé finished his work on fulminate of silver, and Baeyer carried out the researches on cacodyl, which subsequently became famous. After two and one-half years Kekulé received a call in 1858 to Ghent, as ordinary professor.

In this same year came "the two great treatises that have exercised so powerful an influence on chemistry—that on the constitution and metamorphosis of chemical combinations; and that on the chemical nature of carbon. We all know today that the theory of valency is the leading guide through all our science, and no one disputes that its main foundation and its eminent value in organic chemistry are primarily due to Kekulé's idea of the quadrivalency of carbon."

Kekulé put the thought forward with diffidence and only in the interest of integrity and progress. His words were, "It seems proper to communicate these conceptions, because, as it appears to me, they furnish a simple and fairly general expression for the newest discoveries, and because, therefore, the use of them may assist in the discovery of new facts."

In his celebrated Textbook of Organic Chemistry (1859), he insisted upon the facts (a) that carbon is uniformly quadrivalent in organic compounds, and (b) that carbon atoms have the remarkable power, unshared, except in a very limited degree by those of other elements, of linking up together to form chains. This idea, which now seems axiomatic, was then highly original. It was scarcely implied in the older theories and was indeed rather foreign to their point of view. Once grasped, however, it gave the key to the constitution of all organic compounds.

It was not Kekulé, however, who first used the bonds with which

we are now so familiar. The complete analysis of organic radicals down to the arrangement of their component atoms was first attempted by a Scotsman, Archibald Scott Couper, in 1858. Through an unfortunate delay. Couper's contribution was not made public until a month after Kekulé had announced the theory. Because of ill health, Couper was unable to elaborate his thesis. Kekulé had a clear mental concept of the facts which were represented symbolically by Couper.

Kekulé, himself, nevertheless, did not at once begin to write graphic formulas, but rather expressed himself with great conservatism. He closed one essay with these words, "I place no more value on these views than they are worth, and I believe that much labor must still be applied before such speculations can be regarded as anything else than more or less elegant hypotheses; but I believe, too, that at least experimental speculations of this kind must be used in chemistry."

In 1859, Kekulé began to construct graphic formulas, but did not employ Couper's bonds. He drew pictures of atoms of different sizes to represent different degrees of "atomicity" or valency. Kekulé used curious diagrams (Kekulé's sausages) with which we are all familiar. This unwieldy notation was very short-lived, for in 1865, Crum Brown introduced the system, in which each "valency" or unit of combining power is indicated by a line. Thus Kekulé's sausages for oxygen and carbon were represented by Crum Brown by the —O— and $\text{—}\overset{\text{!}}{\underset{\text{!}}{\text{C}}}\text{—}$ which we all know. This is a more elegant and equally intelligible device. By 1865, Kekulé had adopted bonds.

In 1861, appeared the first portion of Kekulé's great textbook which emphasized and illustrated the new views with hundreds of examples. The foundations of modern organic chemistry were therein laid. What is more important, the date marks the time when the great contribution of organic chemistry to the historical development of the science as a whole was fully rendered. The earlier theory had broken down because it had failed to explain the reactions of organic chemistry. Slowly and laboriously through the stages of type theory, there had grown up in organic chemistry the theory of structure which was now destined to become dominant in its turn.

Thus we may assume that Kekulé accounted for the straight chain series of paraffin hydrocarbons. He had linked the carbons with each other. He had developed some building plans. He had not yet formed the three dimensional concept which brings us to organic chemistry.

The architect that his family had hoped Kekulé would become was yet to build.

Let us contemplate discoveries by Kekulé relating to the benzol-ring compounds. His influence and his fundamental ideas disclosed the nature of whole classes of compounds which have been of unusual interest to the people of the world ever since.

Benzene substances had originally received this name on account of a peculiar odor possessed by certain representatives. Later it was found that most compounds so classified exhibited very different properties from those of other organic substances of apparently similar structure. Kekulé found it impossible to devise an ordinary chain formula for its molecule. The constitution of benzene became of fundamental importance. At last it occurred to Kekulé that a consistent explanation was to be found in the assumption that the six carbons of benzene were arranged in a ring united by alternate single and double bonds, and with a hydrogen attached to each carbon. There is a distinct interest in Kekulé's account of how the idea came to his mind:

"I was busy writing on my textbook but could make no progress—my mind was on other things. I turned my chair to the fire and sank into a doze. Again the atoms were before my eyes. Little groups kept modestly in the background. My mind's eye, trained by the observation of similar forms, could now distinguish more complex structures of various kinds. Long chains here and there more firmly joined; all winding and turning with a snake-like motion. Suddenly one of the serpents caught its own tail and the ring thus formed whirled exasperatingly before my eyes. I woke as by lightning, and spent the rest of the night working out the logical consequences of the hypothesis. *If we learn to dream we shall perhaps discover truth.* But let us beware of publishing our dreams until they have been tested by the waking consciousness."

Kekulé thus conceived the idea that in the molecule of benzene the six carbon atoms, instead of forming an open chain, have joined together to form a six-membered ring. The formula is now in any standard chemistry textbook.

Kekulé put forward his well-known benzene theory in 1865. It has been pronounced the crowning achievement, in his hands, of the doctrine of the linking of atoms. It is held to be the most brilliant piece of scientific prediction to be found in the whole range of organic chem-

istry. The conception of closed chains, or cycloids, which Kekulé introduced, has shown itself to be capable of boundless expansion.

Kekulé went to the University of Bonn, in the fall of 1867. He finished his first volume of *Chemistry of the Benzol Derivatives* in the same year. From 1880 to 1887 occurred the publication of the second and third volumes, first as single numbers, prepared with the help of co-workers.

Kekulé always acknowledged the influence of Liebig, Odling and Williamson. Kekulé always distinguished himself as a brilliant and daring thinker, especially devoted to organic chemistry. This branch of the science is indebted to his inspiration for many of its fundamental assumptions. His students spoke of his teaching as lucid; his thinking was called luminous, as well as accurate and concentrated. His language was apt. His delivery was easy and natural. His personality was genial; his humor, happy. He never tolerated slovenly or sloppy work.

His latter years were not productive. Those close to him believed that it was because his researches did not appear to him to be complete. His sense of "finish" and his fastidiousness restrained him from publishing much which he realized fell short of his ideal. Kekulé's greatest service to chemistry remains the development of the theories of molecular structure.

Kekulé died July 13, 1896. His influence lived beyond him. His concept of the carbon ring structure had been truly born of genius. It exercised an influence on all forms of chemistry. Benzene became more than a plaything of science. Modern foundations of constitutional chemistry lie imbedded in the dreams of Kekulé. Researches which Kekulé carried on in his primitive laboratory called for further study with tools fashioned from the results of those early works. In the words Marsh quoted from Landreht, president of the German Chemical Society at Berlin, on the announcement of the death of Kekulé: "This news will be received with sorrow not only by our society but by the whole chemical world. . . . The works which Kekulé has left behind him belong, as we all know, to the basis of all chemistry."

The constant study of the aromatic compounds in the laboratories of the world during the intervening years has served to confirm Kekulé's hypothesis, which may be considered one of the most thoroughly tested generalizations of science. If we remember that perhaps half the total number of organic compounds at present known are derivatives of

benzene we shall form a just estimate of the value of Kekulé's work.

Let us remember that the side-chain theory of Paul Ehrlich may be traced to the studies of Kekulé and Perkin. The Wassermann serology studies owe their existence to the work of Ehrlich. Salvarsan and its counterparts are due directly to the advances made by Kekulé on the benzene ring structure. The latest tools of mankind against disease, the chemotherapeutic remedies of the sulfonamid group owe their existence in their turn to the dye chemistry of Ehrlich.

On the other side of the ledger; we mention poison gas; death-dealing explosives; incendiary bombs. The dreams of Kekulé—what if they had never been translated into molecules dancing in the fertile brain of the boy who became an architect of atoms instead of bricks!

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- Adelman, A. L. *Simplified orthodontia*.
[N. Y.], 1941, 47 numb. 1.
- American Public Health Association. Committee on the Hygiene of Housing. *Housing for health*.
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Minneapolis, Univ. of Minn. Press, [1941], 822 pp.
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Cambridge, Mass., Botanical Museum of Harvard Univ., 1940, 88 p.
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Balt., Williams, 1941, 325 p.
- Zilboorg, G. & Henry, G. W. *A history of medical psychology*.
N. Y., Norton, [1941], 606 p.

PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

DECEMBER 4—*The New York Academy of Medicine*. Executive Session—Reading of the Minutes. ¶ Papers of the evening. Sterility—a] Diagnosis of sterility in the female, Isidor C. Rubin, Clinical Professor of Gynecology, College of Physicians and Surgeons, Columbia University; b] Treatment of sterility in the female, William H. Cary, Associate Gynecologist and Obstetrician to the New York Hospital; c] Sterility in the male, Robert S. Hotchkiss, Assistant Professor of Urology, New York University College of Medicine. ¶ Report of election of Academy Officers.

DECEMBER 18—*The Harvey Society (affiliation with The New York Academy of Medicine)*. The Third Harvey Lecture, "The Adrenal Cortex and Electrolyte Behavior," Robert F. Loeb, Professor of Medicine, Columbia University, College of Physicians and Surgeons.

SECTION MEETINGS

DECEMBER 2—*Dermatology and Syphilology*. Presentation of cases—a] New York University College of Medicine; b] Bellevue Hospital. ¶ Discussion. ¶ Executive session.

DECEMBER 5—*Surgery*. Reading of the Minutes. ¶ Presentation of cases—Cases illustrating the first paper of the evening, George U. Carneal. ¶ Papers of the evening—a] Ambulatory treatment of pilonidal cysts and sinuses (moving picture illustration), George U. Carneal; b] Clinical and physiological studies of the biliary tract in relation to the end-results of operative treatment, Henry Doubilet. ¶ General discussion. ¶ Executive session.

DECEMBER 9—*Neurology and Psychiatry*. Reading of the Minutes. ¶ Presentation of cases—*From the Neurological*

Service of Bellevue Hospital, Foster Kennedy. ¶ Papers of the evening—a] An approach to psychological control studies of urinary sex hormones, George Eaton Daniels; Discussion by Sidney C. Werner (by invitation), David Levy; b] Headache in the localization of brain tumor: a re-evaluation of its clinical significance, Harold G. Wolff, E. Charles Kunkle (by invitation) and Bronson S. Ray. ¶ Executive session.

DECEMBER 11—*Pediatrics—Residents' Meeting*. Reading of the Minutes. ¶ Papers of the evening—a] *New York Hospital*, Osteogenesis imperfecta, Samuel W. Dooley (by invitation); Discussion by Samuel Z. Levine; b] *New York Post-Graduate Medical School and Hospital*, Porencephalic cyst, Vincent Larkin (by invitation); Discussion by John Arthur MacLean (by invitation); c] *Long Island College of Medicine*, An unusual case of dermoid cyst, Joseph Caplan (by invitation); d] *Babies Hospital*, Abdominal pain as an epileptic equivalent in children, David M. Greeley (by invitation); Discussion by Rustin McIntosh; e] *Mount Sinai Hospital*, Congenital skin defect, Herman Anfanger (by invitation); Discussion by Bela Schick; f] *Bellevue Hospital*, Rapid treatment of congenital syphilis, Cornelia Morse (by invitation); Discussion by Charles Hendee Smith; g] *Lincoln Hospital*, An unusual case of lymphosarcoma, Harry V. Lomant (by invitation); Discussion by Harry S. Altman.

DECEMBER 15—*Ophthalmology*. Exhibits 7:00 to 8:00—a] Experimental intracapsular cataract extraction—Hanover's canal; b] Motion pictures in color to illustrate above, Jacob Goldsmith (by invitation). ¶ Executive session—Reading of the Minutes. ¶ Presentation of cases—a] A case of Kaposi's sarcoma, Allan Barnert (by invitation); b] A case of interstitial keratitis and acute dacryoadenitis, C. Gregory Barer (by invitation); c] A

case of keratoconus and atopic dermatitis, Bertram S. Kramer (by invitation); d] A case of surgical construction of a lacrimal passage, Loren Guy. ¶ Papers of the evening—a] The use of the Padgett dermatome in ophthalmic surgery, Byron Smith (by invitation); b] Experiences with acetylcholine, Remarks on the treatment of ocular pain, Edward Hartmann (by invitation).

DECEMBER 16—*Medicine*. Reading of the Minutes. ¶ Papers of the evening—a] Physiological mechanism underlying inhalation therapy, L. Corsan Reid (by invitation); b] The miscellaneous uses of inhalation therapy, Virginia Apgar (by invitation); c] Inhalation therapy; its use for patients other than those with cardiac or respiratory diseases, Emery A. Rovenstine; d] Inhalation therapy in pneumonia, asthma, and pulmonary emphysema: principles and methods, Alvan L. Barach; e] Coordinating gas therapy, Paluel J. Flagg (by invitation). ¶ Discussion.

DECEMBER 16—*Genito-Urinary Surgery*. Reading of the Minutes. ¶ Papers of the evening—a] Renal counterbalance in relation to conservative renal surgery, Louis M. Orr, Orlando, Florida (by invitation); b] Massive hematuria of renal origin, George C. Prather, Boston (by invitation); c] A subtotal perineal prostatectomy and prostatic calculi (moving pictures), Roy B. Henline. ¶ Discussion—Oswald S. Lowsley, Nathaniel P. Rathbun.

DECEMBER 17—*Otolaryngology*. Reading of the Minutes. ¶ Papers of the evening—a] Osteomyelitis of the skull and the repair of osteomyelitic defects in the calvarium, Albert C. Furstenberg, Ann Arbor, Michigan (by invitation); Discussion by Joseph E. King, Andrew A. Eggston. ¶ General discussion. ¶ Executive session.

DECEMBER 19—*Orthopedic Surgery*. Reading of the Minutes. ¶ Presentation of cases—a] A case of post-laminectomy with her-

niation of the cauda equina relieved by spine fusion, Maurice H. Herzmark (by invitation). ¶ Papers of the evening—a] The technique for removal of herniated nucleus pulposus without laminectomy, Edwin M. Deery; Discussion by Alan DeForest Smith; b] Tumors of cauda equina—diagnostic consideration with relation to low back pain—operative results, Ira Cohen, Abraham Kaplan (by invitation); Discussion by Leo Mayer. ¶ General discussion, Alan De Forest Smith, Leo Mayer, David M. Bosworth, John R. Cobb and Mather Cleveland. ¶ Executive session.

DECEMBER 23—*Obstetrics and Gynecology*—*Program presented by The Margaret Hague Maternity Hospital, Jersey City*. Executive session—Reading of the Minutes. ¶ Papers of the evening—a] New method of determination of escape of amniotic liquid, George A. Bourgeois (by invitation); b] Deciduoma of the cervix and endometriosis in pregnancy, Nicholas M. Alter (by invitation); c] Management of premature separation of placenta, S. A. Cosgrove, D. F. Conway (by invitation). ¶ General discussion.

AFFILIATED SOCIETIES

DECEMBER 15—*New York Roentgen Society* (in affiliation with *The New York Academy of Medicine*). Paper of the evening—Tissue changes following irradiation, Shields Warren (by invitation). ¶ Discussion—Fred Stewart (by invitation), Arthur Purdy Stout (by invitation). ¶ Executive session.

DECEMBER 18—*New York Pathological Society* (in affiliation with *The New York Academy of Medicine*). ¶ Presentation of cases—a] A case of Weber-Christian disease, Robert Kritzar (by invitation); b] A case of temporal arteritis, Edith Sproul (by invitation). ¶ Papers of the evening—a] Histoplasmosis, Henry E. Meleney (by invitation); b] The distribution of intimal atheromas in the arteries of rabbits on high cholesterol diets, Sigmund L. Wilens (by invitation). ¶ Executive session.

THE INTER-AMERICA DIVISION OF THE ACADEMY

The Council of the Academy on December 17, 1941 authorized the establishment of an INTER-AMERICA DIVISION of the Bureau of Clinical Information for the special purpose of assisting visiting physicians from the sister republics of South and Central America and the West Indies.

THE NEW YORK ACADEMY OF MEDICINE extends a welcome to all members of the medical profession from other countries of the Western Hemisphere. Visiting physicians are invited to make the Bureau their headquarters while in the city.

THE LIBRARY is one of the largest of its kind in the United States. Its files of American and foreign periodicals are very complete. A bibliographic and photostat service is available at the usual library rates.

MEETINGS. Besides two Stated Meetings of the Academy held each month, there are monthly meetings of the eleven different groups of members organized into Sections devoted to various branches of medicine. Many other medical societies of the city, including a number of affiliates, meet at the Academy.

LECTURES. A series of Friday afternoon lectures on subjects of special interest to the practitioner is given each year, beginning in November.

THE ANNUAL GRADUATE FORTNIGHT is held in October on a subject of outstanding importance in the practice of medicine and surgery and consists of meetings at the Academy, coordinated clinics in selected hospitals, and a large scientific exhibit.

BUREAU OF CLINICAL INFORMATION. The Committee on Medical Education maintains at the Academy a Bureau of Clinical Information where details may be obtained regarding opportunities for postgraduate medical study in Greater New York and also in other cities of the United States.

The Bureau publishes a *Daily Bulletin* which announces the meetings, lectures, conferences, hospital rounds and other interesting medical activities of the day. A *Surgical Bulletin*, issued the previous evening, announces the major operative work of leading surgeons of the city, performed in the clinics of more than seventy important hospitals and other medical centers in the United States.

A Bulletin of Approved Non-Operative Clinics is also published. This Bulletin lists clinics in thirty-three special subjects held in twenty-nine general and special hospitals. Copies of the Bulletins and of catalogues describing postgraduate medical courses offered in Greater New York may be obtained at the Bureau or will be mailed upon request.

DEATHS OF FELLOWS

BOZSAN, EUGENE JOHN: 1130 Park Avenue, New York City; born in Kisuarda, Hungary, December 17, 1889; died in New York City, December 4, 1941; graduated in medicine from the Royal Hungarian University of Sciences, Budapest in 1913; elected a Fellow of the Academy April 7, 1932.

Dr. Bozsan was attending skeletal surgeon at the Morrisania Hospital and associate in general surgery at the Hospital for Joint Diseases. He was a Fellow of the American College of Surgeons, a Fellow of the American Medical Association, a diplomate of the American Board of Surgery, a member of the American Association for the Surgery of Trauma, and a member of the State and County Medical Societies.

DUFFY, JAMES JOSEPH: 862 Park Avenue, New York City; born in Webster, Massachusetts, May 17, 1892; died in New York City, December 13, 1941; graduated in medicine from Harvard Medical School in 1919; elected a Fellow of the Academy November 3, 1927.

Dr. Duffy was assistant professor of radiology at Cornell University Medical College, associate attending surgeon and assistant radiologist to Memorial Hospital, attending surgeon to St. Vincent's Hospital, and consulting surgeon to the New York Infirmary for Women and Children, St. John's Hospital at Long Island City, St. Agnes Hospital at White Plains, and St. Mary's Hospital in Brooklyn. He was a diplomate of the American Board of Radiology, a Fellow of the American College of Surgeons, a Fellow of the American Medical Association, a member of the American Radium Society, and a member of the State and County Medical Societies.

HONEGGER, OSCAR PETER: Lake Mahopac, New York; born in Pittsburgh, Pennsylvania, March 17, 1855; died in Lake Ma-

hopac, December 25, 1941; graduated in medicine from the University of Heidelberg in 1879; elected a Fellow of the Academy June 2, 1887.

NILES, WALTER LINDSAY: 115 East 61 Street, New York City; born in Lebanon, New York, January 2, 1878; died in New York City, December 22, 1941; graduated in medicine from Cornell University Medical College in 1902; elected a Fellow of the Academy February 6, 1908; and served the Academy as secretary of the Section of Medicine in 1911, and chairman of that Section in 1912; as a member of the Committee on Admission, 1915-1921; as a member of the Committee on Public Health Relations, 1917-1929; as a member of the Committee on Medical Education in 1929; as vice-president of the Academy, 1931-1936; as a member of the Board of Trustees, 1928-1932. Again, in 1936, he became a member of this Board and in 1937 assumed its chairmanship, which office he held until his death.

Dr. Niles was professor of clinical medicine at Cornell University Medical College since 1916 and was the dean from 1919 to 1928. He was consulting physician to Bellevue Hospital, New York Infirmary for Women and Children, Willard Parker, Jamaica, Mather Memorial, Southampton and Nassau Hospitals, and attending physician to the New York Hospital. He was a diplomate of the American Board of Internal Medicine, a Fellow of the American Medical Association, a member of the administrative board of the New York Hospital, and a member of the Cornell Medical College Association, the American Clinical and Climatological Association, the Association of American Physicians and the State and County Medical Societies.

PATON, STEWART: 208 Stratford Road, Baltimore, Maryland; born in New York City, April 19, 1865; died in St. James, Long Island, New York, January 7, 1912; received the degree of M.A. from Princeton University in 1886 and graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1889; elected a Fellow of the Academy March 2, 1893.

Dr. Paton was a former associate in psy-

chiatry at Johns Hopkins University and director of the Laboratory of the Sheppard and Enoch Pratt Hospital, Baltimore; lecturer on neurobiology at Princeton University and on psychiatry at Columbia University. From 1926 to 1928 he was consultant on mental hygiene and lecturer on psychiatry at Yale University. He was a trustee of the Carnegie Institution at Washington, a trustee of the Josiah Macy Jr. Foundation, a Fellow of the American Association for the Advancement of Science, a member of the Eugenics Research Association and its president in 1919, and a member of the American Philosophical Society, the American Neurological Association, the American Medical Association and the County and State Medical Societies.

Dr. Paton was the author of several books, among them the "Text-Book of Psychiatry for Use of Students and Practitioners of Medicine," "Human Behavior," "Signs of Sanity and the Principles of Mental Hygiene," and "Prohibiting Minds."

THOMAS, WILLIAM STURGIS: 1141 Fifth Avenue, New York City; born in Poughkeepsie, New York, October 11, 1871; died in New York City, December 21, 1941; graduated from the Medical Department of the National University, Washington, D. C. in 1892; elected a Fellow of the Academy December 15, 1904.

Dr. Thomas was associated with the St. Luke's Hospital for about forty years and served from 1921 until his retirement in 1940 as consultant in immunology and director of the allergy clinic. He was a diplomate of the American Board of Internal Medicine, a Fellow of the American Medical Association, a member of the Society for the Study of Asthma and Allied Conditions, and a member of the State and County Medical Society.

Dr. Thomas was the author of "Textbook on Asthma" and contributed numerous articles to medical journals on allergy, asthma, and allied subjects.

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED
IN THEIR CONTRIBUTIONS

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BULLETIN OF
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MARCH 1942

THROMBO-ANGIITIS OBLITERANS*

EDGAR V. ALLEN

Division of Medicine, Mayo Clinic, Rochester, Minnesota

ALTHOUGH the condition which is now recognized as thrombo-angiitis obliterans probably has been known for many years, the first report on the subject was not made until 1879 by Von Winiwarter. He used the term "endarteritis and endophlebitis" in describing the condition of a man fifty-seven years old who had obliterative arterial disease of the extremities, the symptoms of which had been present for twelve years. After 1879 some isolated reports appeared, but little progress had been made in the knowledge of this disease until the studies of Buerger, which culminated in his report in 1908. Buerger's¹ orderly analysis of a comparatively large number of cases marked an epoch in the study of the disease. His classic report of a study of the arteries and veins in eleven amputated limbs, and subsequent reports, indicate why the disease is commonly called "Buerger's disease," although I prefer to use the term "thrombo-angiitis obliterans," which Buerger gave to this condition in his first publication. The publication of Buerger's book in 1924² marked the beginning of widespread interest in thrombo-angiitis obliterans. Since that time reports concerning this disease have been

* Read before the Graduate Fortnight of The New York Academy of Medicine, October 21, 1941.

frequent and sometimes brilliantly done. A partial list of the important contributors to the study of this disease would include the names of Adson, Duryee, Craig, Barker, Brown, Collens, Hines, Horton, Homans, Herrmann, deTakats, MacGovern, Samuels, Silbert, Wright, Wilensky and several associates of these men as well as others. Although the past has been a pleasing chapter, much remains to be uncovered, and the future must produce even brighter contributions before the book about this disease can be closed.

ETIOLOGY

The cause is unknown. The lesions in the vessels are inflammatory, suggesting a bacterial or viral cause for the disease. Buerger,^{3, 4} with full consent of the patients concerned, produced phlebitis in persons who had thrombo-angiitis obliterans, but whose symptoms at the time were quiescent, by inoculating them with material obtained from acutely inflamed, superficial veins of patients suffering from thrombo-angiitis obliterans. Rabinowitz⁵ found a gram-negative organism in the blood of patients who had thrombo-angiitis obliterans, and believed he produced vascular lesions in rabbits with this organism. These results were not confirmed by Jablons.⁶ Horton and Dorsey⁷ cultured material taken from acutely inflamed veins and arteries obtained at biopsy or at amputation in thirty-four cases of thrombo-angiitis obliterans. Gram-positive pleomorphic streptococci were obtained in pure culture in nine cases, and green-producing streptococci in two cases. Unfortunately, culture of material taken from arteries and veins of amputated extremities of patients who had arteriosclerosis likewise yielded similar organisms, so that the formation of definite conclusions in this study was precluded. Pleomorphic streptococci injected intravenously into thirteen rabbits caused intimal proliferation with thrombosis in two instances. Pleomorphic streptococci were injected into the femoral muscles adjacent to the femoral vessels of forty-two rabbits; intimal proliferation and thrombosis occurred in ten rabbits. Portions of vessels obtained from patients who had thrombo-angiitis obliterans were embedded in positions adjacent to the femoral vessels of twenty-nine rabbits and one dog. Intimal proliferation and thrombosis occurred in seven rabbits, and in one rabbit trophic changes and dry gangrene developed in the toes of the hind feet. This study suggests strongly that streptococci constitute the fundamental cause of vascular lesions in thrombo-angiitis obliterans.

Important support for the belief that the vascular changes are caused by an organism is found in a report of a surgeon who acquired the disease as the result of having a spicule of bone pierce his finger while he was amputating the toe of a patient who had thrombo-angiitis obliterans.⁸ Jews are affected more often than Gentiles, but people of all races and nationalities have the disease. Women acquire the disease infrequently.⁹ Our studies¹⁰ at the Mayo Clinic indicate that the blood in the presence of this disease is essentially normal but there is no uniformity of opinion concerning this point. Syphilis, malaria, typhus fever and the ingestion of rye bread have been implicated, but are not considered to be important today. The smoking of tobacco accentuates the disease and further impairs the circulation as the result of tobacco-induced vasoconstriction, but there is no evidence that the use of tobacco is the primary cause of the disease. Many puzzling questions remain unanswered when the etiology of this disease is considered. Why does the disease affect men more often than women? Is some endocrine influence thereby indicated? Credence in this theory is adduced by the failure of the disease to affect males before puberty and in the years of sexual decline. Why are the lesions encountered much more commonly in the extremities than elsewhere, and particularly in the lower extremities? Why are Jews more commonly affected than Gentiles? Doubtless the true solution of the cause of thrombo-angiitis obliterans will answer these questions.

PATHOLOGIC ASPECTS

Gross changes in the vessels when thrombo-angiitis obliterans is present are characterized early by thickening of the walls of vessels and later by occlusion of the walls by soft, red thrombi which are finally converted into firm, yellowish-white tissue through which minute blood channels course. Adventitia and perivascular tissue become indurated and the artery, vein and nerve are bound firmly together. The earliest microscopic changes are the appearance of lymphocytes in the adventitia and thickening of the intima arising from proliferation of its cells. This stage merges imperceptibly into that which is characterized by thrombosis and complete occlusion of the lumens of the vessels. Thrombi are organized by the ingrowth of intimal cells and new vascular channels are formed in the intima and media. In the end stage, there are marked fibrosis of the adventitia in which a few lymphocytes may remain, per-

meation of the intima by new blood channels and sometimes by increased interstitial connective tissue, and occlusion of the lumens by very cellular connective tissue through which numerous small blood channels course.¹¹

SPECIAL METHODS OF INVESTIGATION

These include oscillometry, arteriography, venography, plethysmography, determinations of temperature of the skin, capillaroscopy, calorimetry, tests of circulation time, tests of claudication time, studies of the oxygen content of the blood and the effects on circulation of anesthesia, as well as other tests. Although each of these special methods of study has added somewhat to the knowledge of thrombo-angiitis obliterans, it is none the less true that in actual clinical practice there is little need for most of them. Their greatest value has been in the securing of knowledge concerning chemical, physiologic and pathologic changes which characterize this disease. Sometimes there is a tendency to rely heavily on special methods of investigation for the diagnosis and acquisition of knowledge concerning progress of the disease. Experienced clinicians, on the other hand, rely almost solely on their knowledge of the symptoms of the disease and the information that can be gained with expert use of the visual and tactile senses. Mechanical methods are poor substitutes for clinical experience.

COMPLICATIONS

In addition to thrombo-angiitis obliterans of the extremities, the cerebral, coronary, renal, mesenteric and other intra-abdominal arteries may be involved. For some unexplained reason, when there are clinical manifestations of involvement of the cerebral arteries such as hemiplegia and hemianopsia or evidence of involvement of the coronary arteries such as angina pectoris or myocardial infarction, the organic changes found in these arteries are only occasionally inflammatory in origin and more commonly are arteriosclerotic in nature. The complications mentioned are serious, and may greatly impair the health or terminate the lives of patients who have thrombo-angiitis obliterans, a condition which ordinarily, at most, necessitates amputation of a limb.¹²

SYMPTOMS

The chief symptoms in thrombo-angiitis obliterans are those resulting

from impairment of the arterial blood supply, since inflammation of arteries and veins, with the exception of what occurs in acute thrombophlebitis and acute arteritis, induces insignificant symptoms. The chief symptoms of impaired arterial circulation are referable to temperature, discoloration, pain and ulceration or gangrene. Coldness of the skin is an invariable accompaniment of impaired arterial circulation, but it should be noted that some persons who do not have thrombo-angiitis obliterans and who have normal arterial circulation also have decreased temperature of the skin. These are the persons in good health who have cold hands and feet. The most characteristic discoloration of the skin in thrombo-angiitis obliterans is the excessive pallor which occurs when the affected extremity is elevated and the excessive cyanotic redness of the skin which is noted on prolonged dependency of the affected extremity. Variable degrees of pallor or cyanosis of the skin as the result of exposure to cold or as the result of emotion are not uncommon. The pain of thrombo-angiitis obliterans may be divided into two types: the so-called exercise pain or intermittent claudication and the "rest pain." Intermittent claudication is a symptom which is pathognomonic of impaired arterial circulation. It is a type of distress which occurs only as a result of exercise and which disappears promptly as a result of rest. Characteristically, it affects the muscles in the calf of the leg. Pain is sharp and shooting and gradually increases in severity until the patient must cease the activity which induces it. Intermittent claudication may affect the ankles, toes, plantar surfaces of the feet, and the forearm, wrist or individual fingers. Pain which is experienced while the patient is at rest may affect the feet or hands, usually the digits, before ulceration or gangrene appears. It is usually of a burning, continuous nature, worse at night, and aggravated by dependency. The pain of ulceration or gangrene often is severe, usually localized to the gangrenous or ulcerated regions, of a stinging, burning quality and associated with hyperesthesia about the lesion. Pain may be remarkably severe and persistent. The pain of sudden arterial occlusion is similar to that observed as a result of arterial embolism. The pain of ischemic neuritis is severe, diffuse, involves large areas and does not correspond to the distribution of peripheral nerves. Paroxysmal exacerbations of excruciating, shooting, pulling, tearing pain occur, extending from one end of the extremity to the other. Paroxysms occur most often at night, and may last for several hours.¹³

CLINICAL TYPES OF THE CONDITION

Slow progression: This is the most common type of the condition. Coldness of the feet, which usually is the first symptom, is followed by excessive fatigue and claudication involving an area such as a single digit, the arch of the foot, wrist, ankle, calf or forearm and by abnormal pallor when the extremities are elevated and by abnormal redness of the extremities when they are dependent. Gangrenous or trophic ulcers may occur.

Absence of progression: In this type mild symptoms of vascular insufficiency (usually excessive fatigue or the pain of claudication) progress slowly for a time and then remain stationary. Trophic changes are limited to proliferation of the nails and increased thickening of the skin over the weight-bearing areas.

Circulatory compensation: This type may belong originally in either of the two types already described. The pain of trophic changes is mild or relieved by medical measures, or the digits may be amputated successfully. Shallow ulcers do not progress and after six months to a year healing occurs. Gradually, other symptoms largely disappear and leave the patient with extremities which are largely adequate for ordinary needs.

Acute fulminating type: Claudication appears relatively suddenly and progresses rapidly. The pain which occurs during rest is severe before gangrenous changes occur and greatly accentuated afterward. Edema and lymphangitis are present around the gangrenous region and slight fever and leukocytosis may occur. Gangrene progresses rapidly; the pain is unbearable and intractable to all measures. Amputation is necessary.

Extensive gangrene without rest pain: This type of condition is very rarely seen. In such cases the diagnosis must await results of pathologic studies.

Venous involvement only: This type of condition is not unusual. The first sign of vascular disease is recurrent superficial or deep phlebitis, which may be present for many years before symptoms and signs of arterial obliterative disease appear.

Normal pulsations in arteries, which usually are palpable: The clinical syndrome usually is that of acute arterial occlusion in one or more digits followed by color changes suggestive of those of Ray-

naud's disease. Gangrene as a rule follows occlusion. Amputation of the digit is followed by healing due to the normal blood supply proximal to the affected regions. Subsequently, other digits may be affected and the obliterative process may progress to a higher level. Diagnosis is dependent on the age, sex and nationality of the patient, the occurrence of superficial phlebitis, the type of pain, the signs of arterial obliteration in single digits, and the finding of organic changes, which are considered to be characteristic of thrombo-angiitis obliterans, in the arteries.

Vasomotor disturbances simulating Raynaud's disease: Clinical evidence in this type of condition is confusing only if the physician fails to recognize the frequent association (30 per cent) of vasomotor disturbances in organic arterial disease. In such cases vasomotor disturbances of the Raynaud type dominate the clinical picture and the organic nature of the disease may be overlooked. The obliterative process is evidenced by signs and symptoms of impaired arterial blood supply. Superficial phlebitis is common.

Associated arteriosclerosis: In this type of condition the signs and symptoms of thrombo-angiitis obliterans are manifested, but there is roentgenographic evidence of calcification of the arteries of the extremities. The radial arteries usually are sclerosed and the age of the patient is at the upper limits, or more than that of the usual patient who has thrombo-angiitis obliterans. Diagnosis is based on a consideration of the age and race of the patient, the occurrence of superficial phlebitis, abnormal postural color changes, the inflammatory zone around the gangrenous ulcer and excessive pain. In many cases microscopic examination of the arteries is necessary before diagnosis can be established.

Severe rest pain without trophic changes: This type is rare. The chief symptom is pain when the patient is at rest, and this pain may equal that which occurs in cases of marked gangrene. The pain is severe, aching or burning and intractable to the usual measures. Examination of the extremities discloses nothing except postural color changes, arterial obliteration and diminished warmth.

Sudden arterial occlusion: Sudden arterial occlusion in thrombo-angiitis obliterans may occur in the course of established thrombo-angiitis obliterans or as the primary manifestation of the disease. The symptoms are similar to those noted in the conventional type of sudden arterial occlusion; namely, a sudden or gradual onset of pain, pallor and coldness or numbness in the extremities.¹⁴

PHYSICAL OBSERVATIONS

1. *Pulsation in the peripheral arteries:* The most important sign of thrombo-angiitis obliterans is the absence or the impairment of pulsations in usually palpable arteries; namely, the dorsalis pedis, posterior tibial, popliteal, femoral, radial, ulnar, and brachial arteries. It should be kept in mind, however, that thrombo-angiitis obliterans may affect the arteries distal to the point at which pulsations ordinarily can be palpated, although this situation occurs infrequently.^{15, 16} There is much to be desired in the matter of general information about determination of pulsations in the peripheral arteries. A comparable situation in auscultation of the heart, for instance, would indicate a chaotic state in the physical diagnosis of cardiac disease. The physician who is interested in the peripheral circulation should, by practice, acquire expertness in the palpation of peripheral arteries.

2. *Postural color changes:* Abnormal changes in the color of the skin accompanying changes in posture indicate occlusive arterial disease and occur in no other condition. To determine what constitutes normal in the matter of the effect of posture on the color of the skin, the physician should study the color of the skin of his own digits. It is a simple matter to elevate one hand over the head for a few seconds and then quickly move it to the level of the waist, alongside the other hand. It is also simple to lie on a bed when preparing to retire and to determine the effect of posture on the color of the skin of the toes by elevating one leg. When the upper extremities of the patient who has thrombo-angiitis obliterans are being examined, he or she should hold the hands above the head and clench them rapidly five or six times; they are then held open for examination. The person who has normal arterial circulation exhibits slight blanching of the skin as a result of this procedure. If there is significant impairment of the arterial circulation, the skin of the palm of the hand and of the fingers becomes blanched excessively. Frequently, it is observed that the skin of one finger or more is decidedly blanched, whereas that of others appears to be normal; also, the pallor may be distributed in an irregular or patchy form. Although blanching of some extent of the color of the skin of the hands occurs normally when they are elevated above the head, the color returns in a regular manner within five seconds after the hands are in the dependent position. If there is prolongation of the time in which normal color returns to the

skin, impaired arterial circulation exists. When a study of the postural color changes in the lower extremities is made, the patient lies in a face-up position, with his legs flexed at the hips at about a 90 degree angle, in relation to his trunk. The patient may support his extremities by locking his fingers behind his knees. The examiner presses blood from the skin of the elevated extremities by repeated firm stroking of the plantar surface of the foot and toes or he asks the patient to alternately flex or extend the toes or to extend and flex the foot at the ankle for about thirty seconds. Normal persons will exhibit only mild pallor, but when there is marked impairment of the arterial circulation, pallor is extensive and marked. After observation of the color of the skin, the person's feet are turned to a dependent position by having the patient sit with his feet over the edge of the bed or examining table. Usually, normal color returns to the skin of the extremities in about ten seconds. If impairment of the arterial circulation of the extremities is marked, color may return slowly during a period of forty-five to sixty seconds or more. Sometimes it returns in an irregular or patchy manner. Less marked delay of the return of color indicates less marked impairment of the circulation. Excessive rubor of the skin when the extremity is in the dependent position also is a manifestation of impaired arterial circulation, but does not specifically indicate impaired arterial circulation. If cyanotic redness of the skin is more marked than it is among normal persons, it constitutes presumptive evidence of impaired arterial circulation. It is usually limited to parts distal to the wrists and to the ankles, but occasionally it extends for a few inches above the ankle.

3. *Temperature of the skin:* It is well to remember that coldness of the skin does not in itself indicate impaired circulation. However, difference in the temperature of the skin of two symmetric parts is important. Thus, if the digits of one extremity are found to be colder or warmer than the digits of the companion extremity, the probability is great that there is a disturbance of the circulation. The same observation is true when a difference of temperature of the skin is encountered among the digits of the same extremity.

4. *Venous filling time:* After elevation of the extremities until the veins on the dorsum of the foot and the dorsum of the hand have collapsed, the extremities are quickly moved to the dependent position. Among normal persons, there is evidence of filling of the veins on the dorsa of the feet and hands within ten seconds. Whenever more than

ten seconds is required for these veins to show evidence of filling, impairment of arterial circulation should be suspected.¹⁷

5. *Phlebitis*: This manifestation usually affects the superficial veins in thrombo-angiitis obliterans, but occasionally the deep veins may be involved. Superficial phlebitis is characterized by red, tender zones along the course of veins and the presence of a palpable thrombus in these veins. After the acute phase of thrombophlebitis subsides, there may be characteristic staining of the skin with blood pigment, which will persist for long periods. Deep thrombophlebitis does not differ from that observed in other conditions.

6. *Gangrene and ulceration*: These conditions are almost always limited to the distal parts; that is, the ends of the fingers and toes. Gangrene may extend, however, to involve almost the entire foot or the entire finger. When localized gangrenous or ulcerating lesions affect more proximal parts of the hand or foot than the digits, the probabilities that these lesions have been induced by various kinds of trauma are great.

DIAGNOSIS

Thrombo-angiitis obliterans should be suspected whenever unexplained gangrene affects the extremities, whenever intermittent claudication occurs, whenever superficial phlebitis recurs and whenever the extremities are cold, discolored or affected by episodes of discoloration. The diagnosis of chronic occlusive arterial disease is based on the finding of diminution or absence of pulsations in the dorsalis pedis, posterior tibial, popliteal, femoral, radial or ulnar arteries. Confirmatory signs are abnormal coldness of the extremities, excessive pallor when the extremities have been elevated for a few minutes, slow return of color and delayed filling of veins when the extremities are put in the dependent position after elevation, and abnormal redness or cyanosis when they have been in the dependent position for a few minutes.

The only condition which offers any great difficulty in differential diagnosis is arteriosclerosis obliterans, which is also a chronic occlusive arterial disease (Table 1).

TREATMENT

Intelligent treatment of thrombo-angiitis obliterans necessitates full consideration of the following conditions.

Thrombo-angiitis obliterans is a self-limited disease. The chief aims

TABLE I

DIFFERENTIAL DIAGNOSIS OF CHRONIC OCCLUSIVE ARTERIAL DISEASE
AFFECTING THE EXTREMITIES*

| Diagnostic points | Thrombo-angiitis obliterans | Arteriosclerosis obliterans |
|--------------------------------------|---|---|
| Age | Between 25 and 45 years | Between 55 and 85 years |
| Sex | Males, 99% | Males, 90% |
| Race | Jewish, 42% | Any |
| Pulsation of arteries | Pulseless, 50% Diminished, 45% Normal, 5% | Pulseless, 50% Diminished, 45% Normal, 5% |
| Claudication | Usually present | Usually present |
| Excessive rubor with dependency | Present | Present |
| Excessive pallor with elevation | Present | Present |
| Gangrene | Common | Common |
| Rest pain | Usually very severe | Usually mild |
| Type of rest pain | Sharp, stinging | Aching |
| Appearance of gangrenous ulcers | Moist, inflamed, discharging | Usually dry |
| Superficial phlebitis | 30% of cases | Absent |
| Roentgenogram of arteries | Usually negative for sclerosis | Usually positive for sclerosis |
| Color changes after exposure to cold | 30% | 15 to 20% |
| Temperature of extremities | Low | Low |
| Edema | Frequent | Infrequent |
| Fats in the blood | Normal | Frequently increased |

*In a table such as this, only the usual situation can be outlined; there are exceptions; percentages are approximate.

of treatment are two: (1) prevention of progression of the disease and (2) establishment of collateral circulation which will be sufficient to maintain life in the peripheral tissues in spite of occlusion of the chief arteries. Occasionally, a physician feels that it is wiser to amputate the lower extremities than to carry out conservative treatment for a long period. Such an attitude neglects two observations: first, amputation can be prevented in the vast majority of instances if adequate medical treatment is carried out; and second, amputation of the extremities does not eradicate the disease, which may continue to progress in other regions, namely, the heart, brain and the intra-abdominal regions. Ade-

quate clinical observation by a number of careful students of the disease has indicated that without doubt much can be accomplished in the medical treatment of thrombo-angiitis obliterans and that under good supervision the incidence of amputation is remarkably low and disability surprisingly slight. These statements do not express satisfaction with the present methods of treatment, for there is much room for improvement. This attitude does, however, take exception to that held by many physicians: that nothing can be done for the patient who has thrombo-angiitis obliterans.

In a consideration of the correct treatment of a patient who has thrombo-angiitis obliterans with gangrenous lesions, ulcers or pain while the limb is at rest, both patient and physician must be thoroughly imbued with the idea that treatment for a comparatively long period is essential if the best results are to be attained. It is sometimes well to point out to a patient that many diseases, such as tuberculosis, for example, require treatment for months, and that thrombo-angiitis may be as demanding of time as the aforementioned disease. If this situation is discussed with the patient suffering from thrombo-angiitis obliterans soon after treatment is begun, he is easily reconciled to slow progress, a state of mind which in itself seems to hasten improvement. It is impossible to state precisely when medical treatment should be abandoned for amputation if amputation is necessary, since the criteria for amputation vary greatly from case to case. In general, in cases in which severe pain cannot be controlled adequately by medical or neurosurgical means or in which gangrenous lesions do not respond to intensive medical treatment for a considerable period, amputation is required. The physician who encounters many patients suffering from thrombo-angiitis obliterans actually encounters three types of conditions, in two of which decision as to treatment is not difficult. In the first prompt amputation is advisable, and in the second amputation need not be considered. For patients who have the latter condition medical treatment and sympathectomy are clearly indicated. In the third condition, however, the question arises at once as to whether or not amputation is advisable. In such circumstances it is best to treat patients conservatively for a minimal period of several weeks. If unsatisfactory progress results from this regime, amputation may be considered. If the treatment causes improvement, it may be continued.

The physician may object at once that thrombo-angiitis obliterans

is a chronic disease and that healing of lesions such as those described does not necessarily mean that cessation of the disease has occurred. He may point out that amputation may be advisable eventually and that there is little reason for deferring the time when such treatment is necessary. Such an attitude prompts the decision to amputate limbs as soon as the diagnosis of thrombo-angiitis obliterans is made. Fortunately, the poor logic of this is apparent, for many patients suffering from thrombo-angiitis obliterans have two fairly normally functioning legs all their lives and many others may be spared one normally functioning leg.

Other physicians may point out that the cost of conservative treatment for a long period is great. It is almost always a good policy to discuss the situation frankly with the patient. If he desires a trial of conservative treatment it seems to me he should have it. If such treatment impresses him as being too costly and too uncertain of producing good results, amputation may be advisable. Too many factors influence the patient to allow the physician to advise him dogmatically. The physician should not allow a poorly founded attitude of pessimism on his part to influence the patient to accept amputation when it may not be necessary. Some patients are treated conservatively too long, but in many instances "too poor" treatment is mistaken for "too long" treatment. I cannot agree that the cost of an intensive but conservative program for a few weeks is too great, if there is a chance of producing healing of gangrenous lesions and quiescence of the disease. I believe that the incidence of amputation for thrombo-angiitis obliterans has been sharply reduced and that it can be further reduced. Earlier recognition, better conservative treatment and less of an impetus toward amputation in many cases are very desirable.

Abstinence from tobacco: The use of tobacco in any form should be denied every patient who has thrombo-angiitis obliterans. It is apparent that it is largely useless to treat patients who continue to use tobacco.

Protection of the extremities: It is important that the extremity or extremities be cared for properly if gangrene is to be prevented. In more than 50 per cent of cases, gangrene is precipitated by some avoidable injury. The patient should do all he can to avoid crushing or bruising of the feet or toes and to avoid scratches, cuts, fissures in the skin, burns, blisters and frostbite. Only comfortable shoes which do not bind or rub should be worn, and the patient should "break in" new shoes

gradually by wearing them about an hour daily. Felt shoes or sheep-skin shoes should be worn in cold weather if the patient is subjected to cold. Diminished activity on the feet is advisable. Patients can carry on ordinary activities, if they are not too strenuous. However, they should attempt to rest the feet as much as possible. In some instances it may be advisable to begin treatment with cessation of all but necessary activities for a month or so. Toenails should be cut straight across after they have been soaked in warm water; corns, calluses and bunions should not be trimmed or incised. Removal of ingrown toenails and minor operations on the toes have caused many instances of gangrene, and these minor surgical procedures should be avoided unless they are performed by a physician who is familiar with the disease. The feet should be washed carefully and gently every day with mild soap and warm water; they should be carefully dried and then 50 per cent alcohol should be applied. If the extremities are excessively dry and the skin tends to crack or scale, they should be rubbed gently with hydrous lanolin or cocoa butter once or twice a day. Preparations containing iodine, merthiolate, sulfonaphthol, carbolic acid, cresol and lysol should be avoided because they may cause ulceration or gangrene. Trichophytosis should be actively treated—but not in the usual manner, because preparations containing salicylic acid may cause ulceration. A safe method of treatment is to soak the feet for half an hour twice daily in a 1:8000 solution of potassium permanganate.

Measures designed to increase the circulation: It may be determined by a reading of the literature that there is a wide divergence between the evidence derived from physiologic studies which indicates improved circulation, on one hand, and the clinical manifestations accepted by various authors as constituting evidence that there was improvement in circulation, on the other hand. This situation has been brought about largely because of the failure of physicians to understand that many diseases are subject to marked remission and accentuation in their natural courses. It is brought about also by the fact that those physicians who are relatively inexperienced, in that they have seen but few instances of impaired circulation, do not have the background which would enable them to interpret clearly the effects of various measures. Finally, confusion is brought about because some authors have advocated vigorously and enthusiastically their own particular methods of treatment when there has been inadequate physiologic foundation for such en-

thusiasm. One need not have been long interested in disturbances of the peripheral circulation to notice that some measures accepted enthusiastically by the medical profession at one time are now largely disappearing from the scene. There is no quality of unkindness in these remarks, for as long as physicians are human beings, enthusiasms will wax and wane and methods will come and go. It does seem advisable, however, for me to make a plea for physiologic evidence that methods which are advocated in the treatment of circulatory disturbances have a beneficial effect upon the circulation. Yet, even physiologic evidence that circulation is improved *temporarily* by specific methods cannot recommend the particular method in question too highly. The best method of treatment would be one which could be shown by the results of physiologic studies to produce permanent improvement of the circulation. Instrumental method A may be shown to improve the circulation temporarily, but it has no virtues over simpler methods of treatment (for example, an environmental temperature of 86° F. [30° C.] which also increases circulation) unless it produces a permanent increase in the circulation. As clinicians, therefore, we are most enthusiastic about a method of treatment which produces a permanent increase in the circulation as shown by physiologic studies, less enthusiastic about methods which produce temporary improvement in the circulation as shown by physiologic studies, and least enthusiastic about methods of treatment which cannot be supported by physiologic studies but which clinically seem to have value. It is well to emphasize herein that data concerning the beneficial results of some particular method of treatment which are based on observation for a long period are of little value, because, as has been noted, there is a distinct tendency for disturbances of the peripheral circulation to regress and progress, and because it is almost always true that no single method of treatment of this disease is carried out. Each physician instructs the patient in the care of his extremities, insists on cessation of smoking, in many instances puts the patient to bed, improves his nutrition and relieves his pain. To this basic groundwork of treatment Doctor A adds method A, Doctor B adds method B, Doctor C adds method C and so forth. Unfortunately, in reporting his results, Doctor A is likely to attribute all improvement to method A, whereas Doctor B is likely to attribute all improvement to method B, and Doctor C is likely to attribute all improvement to method C. This seems to me to be the only explanation for the astonishing correlation of good

results reported from a number of different methods of treatment. Study of the literature reveals that almost all methods of treatment produced good results in a large percentage of cases. This raises the suspicion that it was not the specific treatment alone which produced improvement, but the basic framework of treatment in addition to the specific method of treatment. The most optimistic notes in any consideration of diseases of the peripheral circulation are the great strides that have been made in the progress of therapeutics. These, it seems to me, are more important than the determination of the specific reason for therapeutic improvement.

Local application of heat to the extremities: This may be advisable and may be administered in the form of radiant heat from a carbon filament bulb placed in a cradle or baker. The temperature about the feet should not exceed 100°F. (37.7°C.). Exposure of the extremities to this warmth for an hour two or three times a day is advisable.

Warm sitz baths: These also improve the circulation temporarily.

Postural exercises: These may be helpful, although there is, so far as I know, no evidence that they produce improvement in the arterial circulation. Patients should elevate the extremities for one minute, then place them in the dependent position until rubor becomes maximal, then lie with them in a horizontal position for one minute. These procedures should be repeated five times, two or three times each day.

Contrast baths: These may be advisable. There should be two containers, each large enough to permit immersion of both feet to the mid-portions of the legs. In one container is placed cold water (40 to 50°F. or 4.4 to 10°C.) and in the other, warm water (102 to 105°F. or 38.8 to 40.5°C.). The feet are alternately immersed in each container for one minute for a period of about fifteen minutes, two or three times a day. I know of no evidence that this procedure improves the arterial circulation.

Intermittent suction and pressure (pavex) treatment: In some instances this should be carried out for two or three hours daily.^{18,19} The pressure should be varied, depending on the comfort which the treatment affords and the effects on circulation, but generally a positive pressure of 40 mm. of mercury and a negative pressure of 80 to 100 mm. of mercury are advisable. Ordinarily, a complete cycle should occupy about fifteen seconds. Disappearance of symptoms, healing of ulcers and objective evidence of improved arterial circulation have been reported

to result from this method of treatment. As these reports and others are studied, the reader is impressed with the fact that the physiologic evidence of improved blood flow as the result of this method of treatment is based on a few determinations of the temperature of the skin and on the observation that the flow of liquid through a mechanical schema could be increased by this method of treatment. Cautious question of whether the results on the circulation thus achieved are only temporary seems well founded. Physicians vary greatly in their evaluation of this method of treatment, some are enthusiastic, others believe the method has no virtue. Certainly it is true that in most instances the enthusiasm displayed when the technique first became available has waned, but there still seems to be a place for this method. This type of treatment, as well as intermittent venous compression and passive postural exercises as made possible on the Sanders bed, should be carried out in a room, the environmental temperature of which is about 90° F. (32.2° C.), or in conjunction with the local application of radiant heat.

Intermittent venous obstruction: This technique is considered advisable by some physicians.^{20,21} In developing this method of treatment, Collens and Wilensky utilized the observation of Lewis and Grant,²² who found that an increase in arterial amplitude occurs during venous congestion and that an increase in the arterial flow much out of proportion to the original resting rate occurs when venous congestion is relieved. Evidence is largely or entirely lacking that this reactionary hyperemia does more than repay the debt in circulation which occurs during the period of venous occlusion. Even students of the physiology of the circulation do not agree as to whether or not this method of treatment improves the peripheral circulation. For example, Abramson and associates,²³ who studied circulation with a plethysmograph, found that "In no instance was a sustained increase in blood flow observed in the leg or forearm during or following this procedure." Linton and his associates,²⁴ however, concluded on the basis of results of an experimental study that during the period of venous compression a rather marked increase in arterial inflow occurs. Results of recent studies not yet reported cast grave doubt on the validity of previous observations that intermittent venous occlusion causes an improvement in arterial circulation. It is possible, however, that this method of treatment produces good results in some manner other than by improvement of the arterial circulation. The situation is similar to that which obtains in intermittent

suction and pressure, as far as clinicians are concerned. Some are enthusiastic, others feel that the method has no virtue. Although machines are available which will perform this function automatically, it can be carried out by placing the cuff of a sphygmomanometer about the patient's thigh or arm. The cuff is inflated to a pressure of about 80 mm. of mercury for from two to nine minutes and then deflated for about two minutes. This treatment should be carried out for a minimum of about four or five hours daily.

The Sanders bed: The Sanders bed in brief consists of an ordinary hospitable bed attached to a special cradle so that the bed can be rocked on a transverse axis across its midportion after the manner of a child's see-saw. By means of an electric motor, the bed is tipped on this transverse axis continually, so that the head of the bed is alternately raised and lowered to an arc of approximately 60 degrees. The period of oscillation can be adjusted, so that a complete cycle can be completed within any interval from one to seven minutes. The use of the bed makes use of the old principle of postural exercises described previously.²⁵ Barker and Roth²⁶ noted that by means of this bed pain associated with ulceration and gangrene, pain caused by ischemic neuritis and pain which occurred in the digits without ischemic neuritis or gangrene, was relieved. They thought that in comparison with other mechanical means of treatment of peripheral circulatory diseases, the Sanders bed possesses the advantage of ease of use. As far as I know there is no conclusive physiologic evidence that this mechanical method of treatment improves peripheral circulation, but the clinical results obtained with this type of treatment are occasionally striking.

Hypertonic solutions of sodium chloride: The injection of hypertonic solutions of sodium chloride may aid.^{27,28} In cases of thromboangiitis obliterans without gangrene from 250 to 350 cc. of a 3 to 5 per cent solution are injected, twice or three times a week for about three months; then the frequency of injection is gradually diminished for about six months. In cases of gangrene injection is done three times each week until healing occurs, or until the hopelessness of further treatment has been established. The solution should be injected through a 19 gauge needle at the rate of about 30 cc. per minute. Much controversy exists concerning the efficacy of this method of treatment. Samuels and Silbert obtained excellent clinical results with it; others have believed that the solution of sodium chloride is of little or no benefit. My own doubt and

that of others concerning this method of treatment is based on the conviction that the original premise on which this treatment rests is false; namely, that there is an increased viscosity of the blood in thrombo-angiitis obliterans which can be corrected by the injection of hypertonic solutions of sodium chloride. There is some objective evidence that circulation in the peripheral arteries increases as a result of this method of treatment,²⁹ but Abramson²⁸ concluded as a result of plethysmographic studies that only occasionally did the intravenous injection of hypertonic solutions of sodium chloride improve the peripheral circulation.

Typhoid vaccine: Certainly one of the best methods of increasing the circulation in thrombo-angiitis obliterans is the repeated induction of fever by means of the intravenous injection of typhoid vaccine.³⁰ At the Mayo Clinic we use a vaccine* which contains killed typhoid, paratyphoid A and paratyphoid B organisms. The desired reaction is elevation of the oral temperature to from 101 to 102° F. (38.3 to 38.8° C.). Chill, headache and malaise may result. Excessive elevation of the oral temperature, severe chills, and marked malaise are not necessary and are to be avoided if possible. The quantity of vaccine originally injected contains 15,000,000 to 25,000,000 bacteria for a man and about half this amount for a woman. Ordinarily, each subsequent dose is increased by from 15,000,000 to 25,000,000 bacteria, but the amount injected depends on the reaction. If the reaction to any injection is too severe, the amount subsequently injected should be increased only slightly or not at all. If the reaction is too mild, the quantity next injected should contain 25,000,000 to 50,000,000 bacteria more than did the quantity previously injected. Injection may be done once or twice a week for six or eight weeks, after which a period of rest of several weeks is advisable before another course is begun. Contraindications to the intravenous injection of typhoid vaccine are advanced debilitating diseases, diseases of the coronary and cerebral arteries, a chronic nephritis, mild cardiac insufficiency, active pleurisy or pericarditis, latent or quiescent appendicitis and cholecystitis.³¹ It is our observation, made repeatedly, that the beneficial effects of the intravenous injection of typhoid vaccine persist beyond the period of the fever. Usually, fever which lasts six or seven hours will provide relief of pain for days and it is a rather common clinical observation that lesions characterizing impaired arterial circulation may continue to improve for a period which is much longer than the

*Lederle Laboratories, Inc., New York.

duration of the fever itself. It is my opinion, but one which I cannot develop on the basis of evidence, that the repeated intravenous injection of typhoid vaccine has an ameliorating effect on the course of the thrombo-angiitis obliterans.

Short wave diathermy: This distinctly improves the peripheral circulation, but the effects of such treatment are of short duration.³² Terminals should not be applied to affected limbs.

Heating sleeve and heating boot: This method promises to be of substantial value in the treatment of thrombo-angiitis obliterans.³³ It is a method of inducing vasodilation in the lower extremities by heating the upper extremities, but it has not yet been perfected from a mechanical standpoint.

Miscellaneous methods: The ingestion of alcohol improves the peripheral circulation and may be used judiciously. Papaverine, theobromine, calcium, parathyroid extract—Collip (para-thor-mone), desiccated thyroid substance, sodium thiosulfate, iodides, prostigmine, estrogenic substances, testosterone propionate, sodium chloride taken orally and other agents or methods of treatment have been said to improve the peripheral circulation in thrombo-angiitis obliterans, but in most instances supportive evidence of these claims is lacking.

Sulfanilamide: It has been my impression that *sulfanilamide* is of value in the treatment of thrombo-angiitis obliterans, particularly of that type which progresses rapidly. If no untoward reactions occur, sulfanilamide may be given in amounts of 60 to 90 grains (4 to 5.8 gm.) daily (enough to keep the concentration of the drug in the blood at 6 to 8 mg. per 100 cc.) for a period of two weeks, which is followed by a rest period of two weeks, at the end of which the treatment can be given again. The alternating method of administration may be continued for two or three months if the patient tolerates the treatment well.

Drugs which impair coagulation of the blood: 1. Heparin.—Heparin might be valuable in the prevention of thrombosis which occludes the arteries and veins in thrombo-angiitis obliterans, but difficulty of administration and the cost are prohibitive.

2. Coumarin compound: This preparation, made from spoiled sweet clover (3,3' methylene-bis- [4-hydroxycoumarin]), which prolongs coagulation and prothrombin time of the blood, may be useful in the treatment of thrombo-angiitis obliterans, since it impairs coagulation of the blood and may prevent thrombosis. It may be administered orally

for long periods, and is not expensive.³⁴ Much work remains to be done before any conclusions can be formed concerning the usefulness of this preparation.

Treatment of intermittent claudication: This can be treated by the use of tissue extract. Of these the deproteinated tissue extract* is as good as any.³⁵ It can be injected into the deltoid muscles in amounts of from 3 to 5 cc. If a daily injection for four or five days greatly increases the distances which the patient can walk before the pain of claudication occurs, the injections can be diminished gradually in frequency until a plan is developed which produces maximal therapeutic results. So far as I know, this treatment does not improve circulation, but is intended only to increase the distance the patient can walk before pain occurs.

Treatment of severe pain which occurs while the patient is at rest: Severe pain may affect the extremities when the patient is at rest, when trophic changes are present or when the skin is unbroken.³⁶ In many instances morphine sulfate or dilaudid must be used, but the habituation to these drugs should be avoided. Codeine sulfate is efficacious in many instances. The artificial induction of fever by means of the intravenous injection of typhoid vaccine may produce marked relief. Other measures, such as intermittent suction and pressure, intermittent venous obstruction and the intravenous injection of solutions of sodium chloride, should be tried. When pain does not respond favorably to these measures and the patient loses morale and weight and is unable to sleep, section or crushing of, or the injection of alcohol into, the posterior tibial, peroneal and sural nerves may produce anesthetization of the skin and relieve pain.³⁷ In other instances it is advisable to inject alcohol into the spinal canal for the purpose of affecting the posterior nerve roots.³⁸ Neither of these procedures should be carried out by anyone other than an experienced surgeon. Amputation may be necessary.

Local treatment of gangrene: The wound should be kept clean and the extremity should be soaked for from two to four hours daily in a warm saturated solution of boric acid or a 1:8000 solution of potassium permanganate or an 0.5 per cent solution of chloramine. In some instances surgical cleansing may be advisable, but this should be performed only by an experienced surgeon. It is only rarely that a toe can be successfully amputated, for the incision necessary to this procedure ordinarily does not heal. Contrary to this situation, if fingers are amputated

*Depropanex, Sharpe and Dohme.

the wounds almost invariably heal. In all cases of trophic changes involving the digits patience must be exercised, for it is often necessary to treat patients actively for weeks or months before the gangrenous part sloughs and granulation and epithelization occur. Other measures, such as those mentioned in the preceding paragraphs, should be used. When the ulceration is free from infection and the base is covered with granulation tissue, some of the epithelial stimulants, such as thioglycerol, promote healing. When evidence of infection is present, sulfanilamide may help. When massive gangrene affects an entire foot, amputation ordinarily is the best procedure. In about 80 per cent of the cases healing follows amputation of the extremity below the knee, but it is occasionally necessary to perform reamputation above the knee. The necessity for amputation of the forearm has never been observed.

Treatment of recurrent superficial phlebitis: There is no known method for the successful prevention of recurrence of superficial phlebitis in all instances. In some cases removal of foci of infection may be of value. Acute episodes are best treated by rest in bed and the application of moist, warm packs in which a saturated solution of magnesium sulfate or boric acid is embodied. In some instances roentgen irradiation of the inflamed veins may speed resolution. Sulfanilamide may help.

*Value of sympathectomy:*³⁹ Removal of the sympathetic nerve supply to the extremity is performed for the single purpose of increasing the flow of blood. This procedure does not ordinarily affect intermittent claudication, or prevent recurrence of superficial phlebitis or progression of the disease. It does, however, increase the blood supply to nearly maximum and minimizes the danger that gangrene will necessitate amputation. It should be carried out only when trophic lesions are minimal and healing, or when they are entirely absent and when pain which occurs during rest has been almost entirely relieved or is entirely absent. Whether or not the blood supply can be significantly increased by sympathectomy may be determined by thermometric study of the extremity after the artificial induction of fever by the intravenous injection of typhoid vaccine. Thermocouples are applied to two or three digits of each extremity, one of which is the most extensively involved. Fever is induced by the intravenous injection of a suitable amount of typhoid vaccine. If the increase in the temperature of the skin is markedly in excess of the increase in the oral temperature, or if the maximal cutaneous temperature less the increase in the oral temperature exceeds an

approximate value of 32° C. (89.6° F.) sympathectomy will significantly increase the circulation. Naturally, the kind of treatment to be employed will depend on the clinical syndrome as indicated in the following rough outline:

1. Intermittent claudication and cold, discolored extremities.
 - a. Cessation of use of tobacco
 - b. Prophylactic care
 - c. Tissue extracts
 - d. Sulfanilamide
 - e. Occasional injection of typhoid vaccine
 - f. Sanders bed, pavex or intermittent venous occlusion for two hours daily, or repeated injection of hypertonic salt solutions
 - g. Sympathectomy in place of "e" and "f"
2. Limited ulceration or gangrene with rest pain
 - a. Cessation of use of tobacco
 - b. Hospital care in an environmental temperature of about 90° F. (32.2° C.)
 - c. Sulfanilamide
 - d. Local care of gangrene or ulceration
 - e. Typhoid vaccine
 - f. Use for several hours daily of Sanders bed, pavex or intermittent venous occlusion
 - g. Hypertonic salt solutions
 - h. Section of peripheral nerves if necessary for relief of pain
3. Extensive gangrene or limited lesions which do not heal as a result of weeks of treatment
 - a. Amputation

SUMMARY

Thrombo-angiitis obliterans is a disease of unknown etiology which is characterized by inflammation of veins and arteries, chiefly in the extremities, leading to thrombosis of these veins. The disease produces its detrimental effects chiefly by means of impairment of the arterial circulation. A well-planned program of treatment in which physician, orthopedist and neurosurgeon should participate frequently results in cessa-

tion of the disease and preservation of the extremities. Although many questions concerning this disease remain unanswered and although treatment is by no means entirely satisfactory, great strides have been made in the past decade and a half in an understanding of the disease and in methods of treatment.

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EFFECTS OF RENAL EXTRACT ON
HYPERTENSION*

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AT the present time there are two widely accepted concepts of the pathogenesis of hypertension. According to one of these, which we may designate as the monogenetic theory and which was advocated by Bright¹ and his early followers, the increased peripheral resistance is primarily dependent on renal disease. This concept, once widely accepted, was challenged during the latter part of the last century by numerous writers, including Mahomed,² Huchard³ and Allbutt.⁴ The evidence for their contention was as follows: (a) Hypertension often exists in the absence of clinical evidence of renal disease; (b) Postmortem examination of the kidneys of hypertensive persons frequently reveals only minimal evidence of renal disease; (c) hypertension may develop in the course of certain diseases of the endocrine glands or of the nervous system without evidence of any primary renal disorder. (The increase in blood pressure which sometimes sets in with diphtheritic paralysis and disappears with recovery constitutes a rare but pertinent example.)

The evidence against the monogenetic (renal) theory therefore seemed conclusive and an alternative concept developed. According to this, the polygenetic theory, hypertension was of at least two types: renal; and "essential"—this latter term implying non-renal, cause unknown.

In recent years, attempts have been made to subdivide essential hypertension into a large number of different types.^{5, 6, 7} Such a separation, insofar as it has been successful, has tended to cast further doubt on the validity of Bright's monogenetic (renal) hypothesis. Anyone who bases his conclusion on the available clinical evidence alone must necessarily adopt the polygenetic theory. Such a point of view is, however, much too narrow. It is necessary that we survey all the evidence—experimental as well as clinical. Although temporary hypertension has

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been caused in an occasional animal for many years, it is only within the past decade that it has been possible to induce with consistency a condition resembling chronic hypertension in man. The procedure of subtotal nephrectomy, employed successfully in rats by Chanutin and Ferris⁸ in 1932, did not immediately lead to rapid advances because there was no satisfactory method for repeated measurement of the blood pressure of such small animals. This difficulty has now been overcome.⁹ However, it was the now classical work of Goldblatt and his co-workers,¹⁰ begun in 1928 and published in 1934, which offered for the first time a readily reproducible and feasible method of producing chronic hypertension in the dog, and which indicated the importance of disease of the renal blood vessels as a cause of hypertension. For technical reasons the method of subtotal nephrectomy has not been successful in dogs and the induction of renal ischemia has yielded unsatisfactory results in rats. Hence, the procedure of Page,¹¹ wrapping the kidney in silk and production of perinephritis, which yields chronic hypertension in both species, has been of great practical value.

As the result of these newer studies, and more particularly because of the work of Goldblatt, attention has again been focused on the role of the kidney, and the polygenetic theory with its concept of "essential" (non-renal) hypertension has been seriously challenged. Goldblatt showed that under certain conditions dogs with renal hypertension may present clinical and pathological findings analogous to those found in patients with the so-called essential hypertension. Thus, the very foundation stones of the polygenetic theory were shaken. However, the existence of hypertension clearly related to certain disorders of the nervous system and of the endocrine glands remains to be explained.

Another important result of Goldblatt's work was the demonstration that renal hypertension is independent of renal excretory failure; the evidence being that renal hypertension could exist in the presence of normal chemical composition of the blood. Our own subsequent observations confirmed this conclusion for we were able to show in dogs that bilateral ureteral ligation caused hypertension, while bilateral nephrectomy did not. This conclusion, i.e., that renal hypertension is the result, not of retention products, but of the presence in the body of malfunctioning renal tissue was the starting point of all our subsequent studies.

THE RENAL PRESSOR MECHANISM

Denervation experiments seem to have demonstrated clearly that experimental renal hypertension is not of reflex origin. In searching the literature for a clue as to some possible chemical factor we found that Tigerstedt and Bergmann¹² had described in 1898 a pressor substance of renal origin to which they gave the name "renin." This substance had apparently been overlooked by most subsequent investigators but, following the publications of Harrison, Blalock and Mason,¹³ and Friedman and Prinzmetal,¹⁴ interest in it was revived. During the past four years numerous studies concerned with this pressor substance have been made. Of these the most significant would seem to be those of the Indianapolis^{15, 16} and Buenos Aires¹⁷ groups. Their work indicates that renin interacts with blood serum to form a highly active pressor substance ("angiotonin," "hypertensin") which is thought to be the effective vasoconstrictor agent. Although the view that these renal pressor substances are concerned in renal hypertension forms the basis of a plausible theory in agreement with many known facts, there is also evidence against this view.^{18, 19} Regardless of this question, the only point which concerns us here is that studies on the renal pressor substance first led to the concept of a renal anti-pressor mechanism.

THE RENAL ANTI-PRESSOR SUBSTANCE

The idea that the normal kidney might produce a substance which would be beneficial when administered to animals or patients with renal disease is not a new one, having been advanced as early as 1892 by Brown-Sequard,²⁰ and having been revived more recently by Gomez²¹ in France and Jablons²² in this country. Their concepts have not received general acceptance because these authors offered neither rational *indirect* evidence that such a substance *should* exist nor convincing *direct* evidence that such a substance *did* exist.

In the case of our own work the original indirect evidence that a renal anti-pressor substance should exist was rather strong. It may be summarized as follows:

1. Bilateral nephrectomy causes increased sensitivity to renin. The effect is not due, as Tigerstedt and Bergmann suggested, to lack of excretion because *this increased sensitivity develops slowly one or more days after removal of the kidneys.*²³

2. The blood pressure of hypertensive rats declines during the latter part of pregnancy and rises after delivery. Normal pregnant rats display diminished sensitivity to renin. These effects may conceivably arise from the fetal kidney.²⁴

3. Crude (saline) extracts of normal kidneys tend, on standing, to become less pressor; those from ischemic kidneys tend to become more pressor.²⁵

4. Crude renal extracts containing renin produce progressively less pressor effect upon repeated injection.

5. Senile rats are more sensitive to renin than young adult rats. One would expect senility to be associated with deficiency rather than excess of incretory substances.

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Although the evidence which has been mentioned suggests rather strongly that normal renal tissue exerts some type of anti-pressor action, it is of indirect nature and hence not entirely convincing. Furthermore, this evidence is, in part, based on the assumption that the renal pressor substance—renin—does in fact play a role in the genesis of renal hypertension. This assumption which is supported by some of our own observations and very strongly supported by the observations of Page, *et alii*, is not regarded as entirely convincing by all the workers in this field, nor even by ourselves. Obviously, therefore, the further assumption of a renal anti-pressor substance could not be accepted on the basis of indirect evidence alone. Fortunately, direct evidence is now available. This was first presented by ourselves^{26, 27, 28} and we were gratified when we learned that Page, Helmer, Kohlstaedt, Fouts, Kempf and Corcoran^{29, 30} had arrived at similar conclusions, their work having been performed independently and only shortly after ours. The observations have recently been further confirmed by Jensen, Corwin, Tolksdorf, Casey and Bamman.³¹ Further evidence along somewhat similar lines has been presented by Braun-Menendez, Fasciolo, Leloir and Munoz,³² who found that extracts of various tissues caused enzymatic destruction of "hypertensin;" by Schroeder,³³ who reported decline in blood pressure following the injection of tyrosinase; and by Wakerlin and Johnson,³⁴ who found that the blood pressure of dogs with renal hypertension could be reduced by the administration of renal extracts containing renin.

What, then, is the direct evidence for the existence of a renal anti-

pressor substance? It consists in a demonstration that the blood pressure of animals with renal hypertension may be reduced by the administration of an extract prepared from normal renal tissue. We have obtained this result in approximately one thousand rats and in about a score of dogs. In our first experiments the material was administered by injection but, after having discovered the effectiveness of the extract when given by mouth, we have employed the oral route almost exclusively. It is now generally recognized that a number of non-specific noxious substances derived from animal tissues may exert a depressor action when administered parentally. Probably some of the reductions in blood pressure observed by earlier investigators, using crude extracts of various tissues, are to be ascribed to such an action. None of these extracts of previous authors have been shown to produce decline in blood pressure when administered by mouth. Although oral administration of our renal anti-pressor substance requires much greater quantities of the extract, it renders the results more convincing by reducing the likelihood of obtaining—from impure extracts—declines in blood pressure due to non-specific or toxic substances.

One naturally wishes to know whether the extracts containing the renal anti-pressor substance are of any value in treating patients with hypertension. In May 1939, we reported two patients who had exhibited decline in blood pressure following the administration of such extracts.²⁶ In June 1940, observations on five patients were presented.²⁸ Since that time we have treated only four additional patients. (The number is small because of the expense and the technical difficulties involved in preparing the huge quantities of the extract required for human use.) Of these four patients one was in advanced uremic coma and died within a few days after treatment was instituted. The decline in blood pressure which this patient exhibited would probably have occurred as a terminal event in any case and no significance can be attached to it.

A second patient received large amounts of an active extract orally but no decline in blood pressure occurred. Whether this negative result is to be ascribed to destruction in the gastrointestinal tract, to failure of absorption, or to refractoriness of certain types of hypertension to this form of therapy is uncertain.

The third patient was a young man with glomerulonephritis who was carefully studied during several months in the hospital. On two separate occasions a moderate decline in blood pressure associated with

subjective improvement occurred following administration of renal extract. The decline in blood pressure endured for two or three weeks after therapy was withdrawn. The blood pressure then gradually ascended to the original level and again declined when therapy was resumed and rose after the extract was discontinued.

The results in the fourth patient seemed to be remarkable. This young man had a typical picture of subacute glomerulonephritis in the nephrotic stage. He had marked papilledema and was practically blind. During the oral administration of renal extract his albuminuria decreased markedly, diuresis occurred, edema diminished and the blood pressure declined to a level only slightly above the normal. The vision improved rapidly so that he was able to read large print, whereas, previously he could not even see fingers, much less count them. However, since his illness was of only three months duration it is possible that the improvement in this patient may have been coincidental. Such an interpretation may be favored by the fact that the improvement in this patient was still manifest several months after treatment was discontinued. Since, in this case one might conclude either that the improvement was entirely spontaneous or that the extract was markedly beneficial, it is perhaps wisest to draw no conclusions.

We ourselves do not regard our results on patients as being convincing. The technical difficulties are great, many pounds of kidneys are required daily in order to treat one patient; and there is even doubt as to whether the active principle is absorbed at all in some subjects. Since, in rats, the preparations seemed to be several times as active when injected, as when administered orally, we are devoting our attention to the fractionation of the extract in an attempt to secure a potent nontoxic concentrate which can be injected without local or systemic reactions. Until this can be accomplished we prefer to draw no conclusions concerning the possible value of renal extract in patients.

The present status of the problem may perhaps be compared to that of the ovarian extract a dozen years ago. At that time the capacity of such extracts to produce physiological effects in small animals had been definitely demonstrated but the amount of the active principle present in the ovaries is so small that many years would have elapsed before the value of these preparations could have been demonstrated beyond question in patients, had not other sources been found from which the hormone was obtainable.

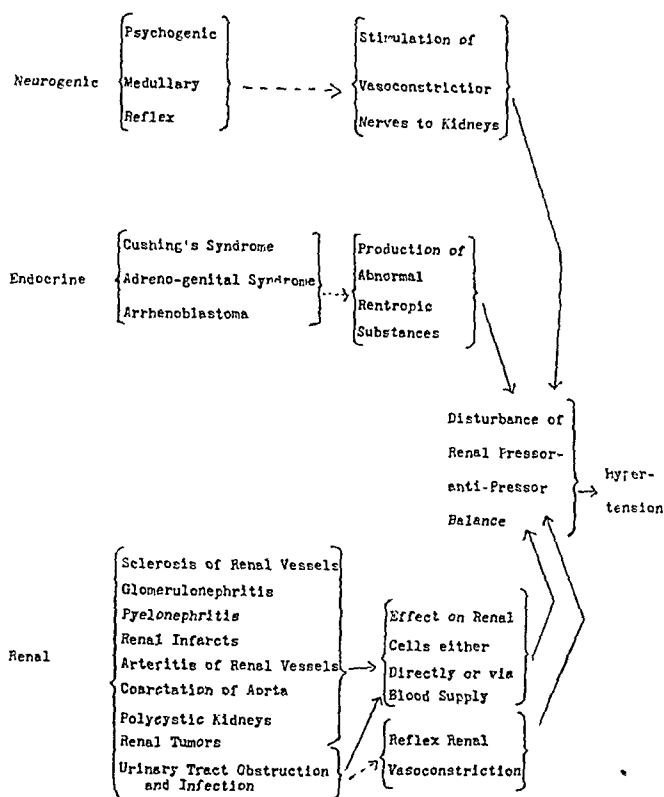


Figure 1

One would naturally wish to know whether these observations on the renal anti-pressor substance have any bearing on the general concepts of the genesis of hypertension. In this regard it may be emphasized that apparently favorable results have been obtained both in patients with "essential," and in subjects with renal hypertension. In view of this observation, as well as the others which have been mentioned, it may be justifiable to suggest that both the monogenetic theory and the polygenetic theories are partly true but that both are incomplete. Our present conception, which is still based largely on hypothesis, is illustrated in Figure 1.

There is some evidence, which can not be regarded as conclusive, that experimental neurogenic hypertension (e.g., that resulting from carotid sinus denervation or from intracisternal kaolin injection) is abolished by renal denervation and also that hypertension of this type may respond to the administration of the renal anti-pressor substance. It would therefore seem logical to infer that hypertension of neurogenic

origin, as observed in patients, may be mediated through a renal mechanism. (Obviously, this concept refers only to chronic hypertension and not to temporary elevation of blood pressure of nervous origin.)

The endocrine disorders associated with chronic hypertension are all characterized by the production of abnormal steroid compounds. Since it has been shown in experimental animals that many steroidal compounds exert a renotropic action and produce hypertension, it is not unreasonable to assume that the hypertension occurring in the endocrine disorders cited in the diagram is mediated through the kidneys.

Although the complete details of the mechanism of the chronic hypertension which results from primary affections of the kidney are still under discussion, few question its humoral basis and it is presumably brought about by a deficiency, either relatively or absolute, of the renal anti-pressor substance. Whether those disorders of the lower urinary tract which are sometimes associated with hypertension operate mechanically through effects on the renal blood vessels and parenchyma, or reflexly through a nervous mechanism analogous to that responsible for acute reflex anuria is still debatable.

If one accepts the validity of the concepts which have been outlined, it is possible to harmonize the monogenetic and the polygenetic theories of the pathogenesis of hypertension. It is quite possible that a number of separate primary disorders, whether of the nervous system, the endocrine glands, or of the kidneys, or of unknown origin, may all cause hypertension by acting on a fundamental renal mechanism.

SUMMARY

The various theories which have been proposed to explain the pathogenesis of chronic hypertension in man are analyzed in the light of recent experimental findings in laboratory animals. The variety of clinical states which are associated with hypertension suggests a diversity in the mechanisms (polygenetic theory) responsible for hypertension. Recent experimental studies point strongly to the kidney as the site of the disorder (monogenetic theory). A schema is presented which attempts to harmonize these two divergent viewpoints and which, although hypothetical in many respects, appears to be in accord with available data.

Extracts of normal kidneys when administered to animals with experimental renal hypertension cause decline in blood pressure. The

administration of such extracts to a few patients with either renal, or so-called "essential" hypertension, has been followed in certain instances by decline in blood pressure and by clinical improvement. The possibility that the changes observed in patients may have been of spontaneous, rather than therapeutic, origin has not been completely excluded.

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Although the results of the administration of renal extract to patients are perhaps of significance in regard to the mechanism of hypertension, they have no therapeutic importance at the present time. Until methods of obtaining a larger yield of the active principle and of producing purer extracts can be developed the results obtained with renal extract will be only of theoretical significance.

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THE USE OF INSULIN IN ITS VARIOUS FORMS IN THE TREATMENT OF DIABETES*

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THE use of insulin in its various forms in the treatment of diabetes is in its infancy. Insulin is not at all adequately appreciated and its application is not understood. The treatment of diabetes with insulin is still crude. To paraphrase Lukens' thought, we have constantly been trying to see how many diabetics we could treat without insulin rather than how many we could treat with it. What proportion of patients now secure its benefit, no one can say, but of the 14,153 diabetics registered in Berlin, according to Umber,¹ in 1940, the number using insulin was 37 per cent. In our own hospital practice 87 per cent received insulin and in the office practice 80 per cent. Moreover, few of us, who thank God and Banting and Best for the discovery of insulin and daily watch its miraculous action with our patients and are prescribing it more and more, would claim that we are using it to the greatest advantage or in the best way. And now, just before I shock you, as I myself was shocked, by recounting the dreadful examples of the disuse or improper use of insulin, I would call to your attention, in partial apology for the medical profession, that great discoveries in medicine percolate slowly. Opposite the hill on which I write these words is Charlton, in Worcester County, where was born one Thomas Morton who held his ether cone at the Massachusetts General Hospital for the first time in 1846. Yet two generations later in that same institution Harvey Cushing actually felt like giving up his medical career when the patient he was etherizing expired. The following recital is sombre, will be painful, but I believe should be said and I dare to do it because I report all my known diabetic deaths and strive to point out my own egregious mistakes. Do not be discouraged. We learn from our errors, and if we honestly describe them, one needlessly dead patient may lead to the saving of thousands of lives.

I repeat, insulin is not adequately used by the medical profession. A

* Read October 2, 1941 at the Stated Meeting of The New York Academy of Medicine.

physician of national reputation in the Middle West wrote me recently that within a period of four weeks this summer he had treated four doctors each with diabetic coma. This has happened in the face of the fact that a few years ago with the help of the Metropolitan Life Insurance Company it was possible to state that diabetic doctors from a study of their subsequent course lived longer than diabetics as a whole and that among all patients the mortality from diabetic coma has dropped from 63.8 to 3.6 per cent.

Upon one afternoon in September, 1941, three cases especially attracted my attention. The first concerned an interview with a friend of a diabetic child, living nearly two hundred miles away in a city of about 50,000 population, whose glycosuria was said to be of little account despite the child's hunger, loss of weight and strength. In the course of the consultation during my endeavor to see how I could coöperate with the doctor, the child's friend produced a bottle of a well-known quack medicine with which the child had been treated. A week subsequently I saw the frail, crying child arrived in acidosis with 9.0 per cent glycosuria, and this occurred nearly twenty years after the beginning of the use of insulin with human beings. That same afternoon another patient disturbed my equilibrium, because she was such a heavy weight for the modest elevator which brings patients to my office. Some months before, she was given insulin and told to protect the insulin with orange juice. During the period her weight rose from 225 pounds to 275 pounds. The third instance was a woman in middle life whose urine showed 4 plus diacetic acid and 6 per cent sugar. She had been given insulin about five weeks before, but the doctor, instead of instructing the patient, administered it himself twice a day, then died, leaving her without a knowledge of taking insulin.

During 1941 there have been at least eight deaths among our supposedly twelve hundred living patients with onset in childhood. Of these deaths at least two appear to me to have taken place because of hypoglycemia unrecognized and insufficiently treated.

Have I not told enough to demonstrate that the treatment of diabetes with insulin is in its infancy and that the use of insulin is inadequate and not understood? Let us now turn to a brighter picture.

The proof of the usefulness of insulin is best shown by the better maintenance of nutrition by diabetic children. It is so good, in fact, that their identity among their comrades is concealed. As a corollary to

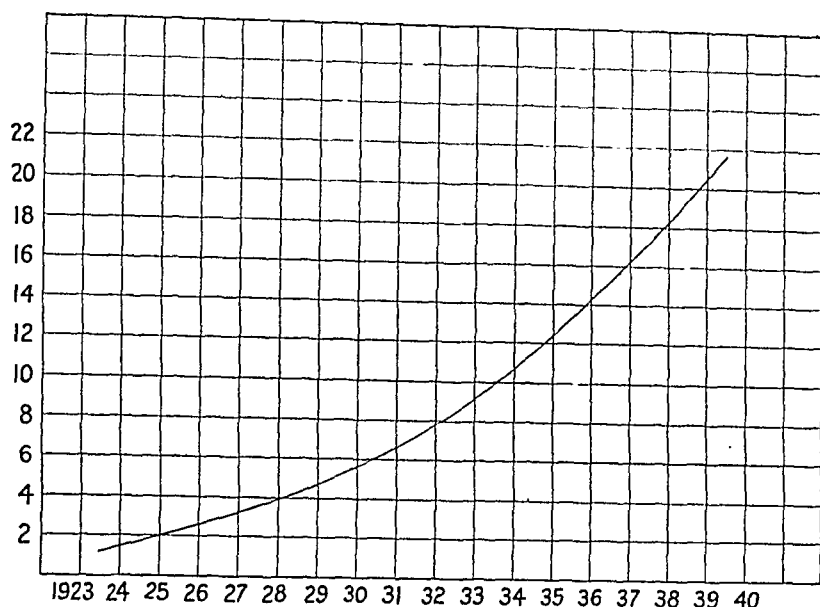


Chart 1—Nothing interferes with the increase in the distribution of insulin. (Courtesy, C. H. Best.)

this is their greater resistance to disease, not only to the chronic infections like tuberculosis, but to the acute infections and those requiring surgical intervention. By no means are these effects confined to children. The ability to bear the brunt of another disease running concurrently with diabetes is obvious to all. Whether neuritis and certain other complications are more frequent or less frequent is concealed by the longer duration of the disease and consequent longer exposure of the individual. Arteriosclerosis has ceased to appear as a rule at the end of five years, although it ranks first as the cause of death in diabetes.

Bodily efficiency and ability to work have increased so much since the use of insulin that the morale of the diabetic is completely changed.

The value of insulin is acclaimed by the uninterrupted increase in sales of the drug. So far, nothing has interfered with this upward tendency. Despite the subcutaneous method of administration which makes so many apprehensive and delays its employment, there is an increasing readiness to use and inject it.

The efficiency of treatment and the standardization of the disease are more readily accomplished with the aid of insulin than in any other manner. It is far simpler today to compare results of different methods of treatment, thanks to insulin.

The diffusion of knowledge of the physiology and the pathology of diabetes has greatly expanded since the introduction of insulin and constitutes one of the long range benefits from its discovery. It has raised the platform of knowledge of diabetes and metabolic processes in the body in the minds of millions of people. It has created respect for scientific work in laboratories such as perhaps no other achievement.

I will not burden you with statistical evidence showing the improvement of treatment of the disease save for a few examples. The first group of these is made up of the 83 cases who were the first to receive insulin at our hands. Of them 50 have died, and the average duration of life of these fatal cases was 10.3 years. Thirty-three still remain alive and the average duration that they have attained is 20.7 years. Since the previous computation one year ago there have been no deaths.

The second group. Fifty of our diabetics under the age of 40 years with a duration of the disease of at least five years were studied in 1930 intensively by H. C. Shepardson of San Francisco. Of this group, 12 have died and their duration of life has been 13.3 years. The duration of life of the surviving 38 on the average is 19.8 years. During this last year there have been no deaths.

The third group. Diabetes with onset in childhood of twenty or more years' duration. At present there are sixty-two children eligible for this classification. Of this number two have died after a duration of the disease of twenty years and the causes of death have been coma and streptococcus sepsis. Of the remainder, we have thus far definite information that 59 are living in 1941 and have reason to suspect that the one untraced also is alive, because they were all traced in 1940. It is very much more difficult to trace a diabetic child now than formerly, particularly those with such long duration, and obviously the girls because so often names are changed.

The fourth group. The total number of fatal cases between January 1, 1937 and March 29, 1940 which we chance to know was 927. For these the average duration of life was 12.5 years. Prior to the discovery of insulin my patients lived 6 years and their age at death was 46.7 years instead of 64.8 ending in 1940. The life expectancy for a ten-year-old diabetic child as calculated for me by the Metropolitan Life Insurance Company was such that he would reach his fiftieth birthday and, in fact, for all ages was approximately two-thirds that of the population as a whole. The number of patients now living for 12 or more years is so

large that it obviously makes the computation of statistics unusually difficult, because of change of residence or name.

Statistics relating to pregnancy are striking. To the mother pregnancy carries very little greater mortality than for non-diabetics. For the offspring, under most modern conditions of treatment, the viability is about 90 per cent for those whose mothers have had prolan determinations which were normal or if abnormal were corrected by hormones.

Diabetic mortality statistics I fear may grow less accurate as years advance. This is readily explainable because so many of the patients succumb to diseases which are not definitely related to diabetes and thus the diabetes fails to appear on the death certificate and also because the disease diabetes is so mild at death that it may not claim recognition at all, even by the family physician. Thus far, the incidence of diabetes has been almost steadily rising, and from twenty-seventh as the cause of death in 1900 for the United States it was ninth in 1938, but in 1939 became eighth with the prospect of displacing both pneumonia and tuberculosis in the near future. It would then become sixth as the cause of death and only exceeded by cancer, arteriosclerosis in its various sites, and deaths by violence. Plainly, diabetic statistics in the future must depend upon those of private clinics, and those especially sought by detailed investigation. Insurance companies could help to disclose the knowledge of the causes of death of diabetics perhaps more readily than is possible in any other way than those just cited. I fear that we may become blinded to the growing importance of the disease by a halt in its mortality incidence. Thus, in the seventh month of 1940 the death rate from diabetes among the Metropolitan Life Insurance Company policy holders in their industrial departments was 30.2 per 100,000, but in 1941, 29.3 per 100,000. I confess I shall become skeptical about the accuracy of diabetic statistics if the incidence does not go up. My experience in comparing the reputed incidence of diabetes in Arizona with that in Rhode Island² taught me that although in one state the reported incidence is 10 compared with 42 per 100,000 in the other, I was able to satisfy myself by detailed investigation that the actual mortality rate in the two states was approximately the same, if one made allowances for age and sex of the inhabitants on the one hand and the ability to secure data from them on the other.

And right here may I put in a plea for more autopsies, or rather published records and analyses of autopsies of diabetics. Shields War-

ren³ in the second edition of his book bases his studies upon 486 autopsies. Weichselbaum⁴ in 1901 reported 18 cases. Gibb and Logan⁵ in 1929 reported 147 autopsies. When we recollect that in 1938, 31,037 people died with diabetes in the United States and in 1939, 33,395, the paucity of data upon which to base conclusions upon the pathology of the disease is evident. How many autopsies were reported, and analyzed, upon diabetics in New York City in 1940? The new American Diabetes Association and its subsidiaries can be of great service in collecting data of this type.

Regular Insulin. Until the present, most of the advantages of the treatment of diabetes with insulin can be ascribed to regular insulin. Protamine insulin came into use during 1936, but since that date the average age at death of my patients has advanced only from 63.6 to 64.8 years, and the duration of the disease from 12.1 to 12.5 years ending March, 1940. There are certain exceptions to the above statements. It is true coma has dropped still further, but it was already low.

Regular insulin exerts an action for six hours, and save with those patients whose disease is so mild that the blood sugar falls to normal during the night it is necessary to give four doses in twenty-four hours to control it. Boyd⁶ has shown that even hepatomegaly could be obviated if such a general rule was followed. If only one type of insulin was available one would choose regular insulin, or rather its counterpart, crystalline insulin, which apparently acts just the same only for about an hour longer. If one wished adequate control of the disease, save in those mild cases becoming sugar-free during the night, the largest dose would be given before breakfast and attempts made by rearrangement of the diet to avoid a dose at noon, the second injection before the evening meal, and the third toward midnight, consisting of a few units varying with the urinary tests. Each dose omitted, even that at noon would mean that doctor and patient were contented with a passing mark and were not striving for a Phi Beta Kappa key or, better, perfection. Perhaps 24-0-18-2 would represent the dosage which has generally been used by those physicians almost meticulous in the care of their patients, but for complete protection a slight amount at noon would be generally needed.

In diabetic coma the need is for insulin, and the dosage rises the longer the duration of the coma before treatment begins and the greater the severity of the acidosis. The sky is literally the limit, and just because one does not recover with 500 or 1000 units is no excuse for not admin-

istering 1500 or 2000 units if the case warrants. The need in coma for liquids to combat dehydration stands next to the need for insulin, and this, too, varies widely from an average of 2000 cubic centimeters to the exceptional patient who recovered with 11,000. We never have had reason to fear circulatory collapse following the parenteral administration of insulin.

By no means is the short duration of the action of regular or crystalline insulin its only drawback. As a matter of fact, at least for approximately half of its effective period, it is over- or underactive, because a preliminary time is required for it to exert an adequate effect and later despite careful adjustment of food with the insulin, hypoglycemia can easily result.

The disagreeable qualities of any insulin are included in the action of regular insulin. First and foremost come insulin reactions. In not a single instance since the introduction of insulin on August 7, 1922 have we known of a death clearly due to hypoglycemia in a patient treated with insulin who was already in, or brought into the New England Deaconess Hospital. One unconscious patient was admitted. He remained unconscious for days and finally died, but we are still in doubt after the autopsy as to whether that patient died from hypoglycemia. On the other hand, insulin reactions certainly are responsible for more deaths from diabetes than are recorded on death certificates. This is not because there is falsification of the death certificate, but rather due to an error on the part of a physician. In a recent article in the *Medical Clinics of North America*, I have discussed this in detail. My experience has led me to conclude that if recovery during a possible insulin reaction does not occur within 15 minutes the patient should be taken to a hospital unless facilities for tests of the blood are available in the immediate vicinity.

The difficulty in distinguishing between an insulin reaction which has gone on for an indefinite time and late diabetic coma is very great. In that same article four or five needless deaths from hypoglycemia are described. It is a safe assumption that no insulin can be invented which will not lead to an insulin reaction provided exercise is unusual and diet omitted. Insulin atrophies occur with regular insulin and with protamine zinc insulin with uncertain frequency. Whether they will develop with the other types of insulin, one can tell only when a large number of cases have been treated with these. Notable insulin atrophies occur per-

haps in one in a hundred or even one in fifty cases and still more frequently in children. Consequently, one must have experience with several hundred, indeed several thousand cases with the newer types of insulin before a conclusion can be drawn regarding the same. Insulin indurations or lumps depend almost entirely upon neglect to follow the standard rules for treatment, namely, to distribute the dose of insulin over various sections of the body and never to administer two injections within an inch of each other in the course of a month.

Insulin Sensitivity. Unquestionably I think it can be said that insulin sensitivity is somewhat less with crystalline insulin than with regular insulin. Whether it will be entirely absent with the other types of insulin to be discussed later will depend upon the accumulation of hundreds or thousands of cases. At any rate, in the last few months we have been less concerned about insulin sensitivity, because apparently one can relieve the severe forms of it very simply by beginning with injections of $1/1000$ part of a unit and increasing by $1/1000$ of a unit at each injection, four times a day. As a rule, after 24 hours it will be found that the rate of increase can be accelerated so that within two or three days it is possible to give several units. During this interval of waiting, one treats the patient as in the days before insulin was discovered by lessening the need for calories by rest, by curtailing nutrition through decrease of fat, reduction of protein to a gram or $\frac{2}{3}$ of a gram per kilogram body weight and lowering carbohydrate, at least to 100 grams in 24 hours.

The outstanding effects of regular insulin are shown best of all in the decrease of deaths from coma by prevention or actual cure and, second, by the lengthening lives of diabetics with onset in childhood.

Crystalline insulin is a solution of zinc insulin crystals. Its action is essentially the same as that of regular insulin with one exception, namely, the duration of the effect is about one hour longer. The type of reaction is essentially the same as that caused by regular insulin. Insulin atrophies can occur. Insulin induration will develop in the careless patient. Insulin sensitivity likewise appears although possibly a trifle less than with regular insulin. It can be overcome by the same measures as recommended above. To me, the effects of crystalline can be summed up in the words that it is a purer drug than regular insulin, has all the advantages of the former with somewhat less of its disadvantages, costs no more and with the same frequency of doses a patient can be controlled for an additional three hours in the 24 hours.

Protamine Insulin and Protamine Zinc Insulin. Hagedorn revolutionized the treatment of diabetes when he added protamine to insulin and thereby doubled the duration of its action. This was quickly changed by Scott, who, by the addition of zinc doubled again the action of protamine insulin, prolonging its effect for fully 24 and possibly even to 48 hours. At any rate, Marble and Bailey found that satisfactory tests could not be undertaken with a new type of insulin until protamine zinc insulin had been omitted for that period. Protamine zinc insulin reduced the number of injections for the patient, made treatment safer, simpler and more agreeable, encouraged more doctors to give it and patients to begin it, kept the disease under control for a longer period, and in cases of moderate severity one dose a day has been sufficient. The overlapping effect from day to day of protamine zinc insulin and the necessity of taking a few days' time to transfer a patient from crystalline insulin to it I consider of no importance. Two or three days will not count in the length of a diabetic patient's life today. Furthermore, most of us today begin treatment with protamine zinc insulin and therefore there is no time lost in the transfer.

Protamine zinc insulin acts while you sleep and that is not a disadvantage if a patient understands it and guards against it by a supplementary meal on retiring. Certain patients do not need this. It is particularly adaptable to severe diabetics who day and night show glycosuria from endogenous metabolism. Protamine zinc insulin, therefore, with quick-acting crystalline insulin administered before breakfast to help utilize the food consumed, gives us a method for treating the severest diabetics and I do not worry about its application to the milder. As a matter of fact, among three hundred hospital diabetics, treated in succession in 1938, for whom McDaniel of our clinic compiled for me the intake of insulin, it was found that 10 per cent required no insulin whatever, 39 per cent were regulated with an average dose of 22 units of protamine zinc insulin, whereas 50 per cent required both crystalline and protamine zinc insulin before breakfast, 13 units of crystalline and 39 units of protamine.⁷ Reading the very excellent article by Marks⁸ which appeared in the *Medical Clinics of North America* of May, 1940, one can learn how in perhaps considerably more than our 39 per cent, it is possible by adjustment of diet to regulate the patient with a single dose of protamine zinc insulin. I commend this article to your attention. On the other hand, I must say that of the cases cited with

successful treatment with a single dose, not one was a child, and we have found that with our children it was practically always necessary to give a quick-acting insulin along with the protamine zinc insulin.

Adjustment of the diet of the insulin-using patient is desirable. Practically all our patients for years have had approximately carbohydrate one-fifth for breakfast, two-fifths at noon and two-fifths at night, taking away 5 or 10 grams of carbohydrate from their noon or night meal to use between meals or upon retiring. This was for those cases in which it seemed likely that a low blood sugar would arise during the night. We have taken advantage of Pollack's advice and given more protein with that retiring meal.

Protamine zinc insulin is well adapted for use during infections, and at the time of surgical operations. One does not attempt to control the entire disease with protamine zinc insulin on such occasions, but in protamine zinc insulin one exerts a steady, partial control of it and can supplement it with quick-acting insulin every four or six hours according to tests of the urine.

Since the introduction of protamine zinc insulin it is a fact that we have given up our wandering diabetic nurse, going from home to home, because we no longer needed her. Already I have called attention to the lessening number of patients with diabetic coma. Furthermore, those patients who do develop coma develop it because of gross irregularity for which protamine zinc insulin could in no way be held responsible. The disappearance of hepatomegaly was striking. Marble, White and all our group felt almost sorry that we did not have a chance to try lipocaic, because when protamine zinc insulin was introduced, the large livers of our children right under our fingers and eyes by x-ray went back to normal. Dwarfism in diabetes is now a very, very rare occurrence. Of course this may be due in part to the more liberal diets which we give, stimulated in their use by reports from clinics in Vienna, California and your own Geyelin.

A word more about office treatment. Today it is extremely difficult to secure an adequate number of beds at the hospital for our diabetic patients. The number, therefore, treated in the office of necessity has definitely increased. Willingness to do this is largely due to a feeling of greater safety, as well as ease of administration, of protamine zinc insulin.

From all these favorable remarks about protamine zinc insulin, you might infer that I do not realize its disadvantages. It is unfortunate that

protamine zinc insulin is a cloudy mixture. To me it is extraordinary that protamine zinc insulin works as well as it does when one considers that unless the bottle is manipulated in exactly the same way for exactly the same number of seconds and the insulin withdrawn in the same period of time, one must have variation in the actual content of the mixture injected. Any type of insulin which depends upon the injection of solid particles in suspension in a liquid admits of improvement. The second objection is the considerable number of patients who show localized reactions lasting from a few days to a few weeks following its use. Almost invariably these will disappear if one persists in treatment, but I have seen cases in which we have changed from one type of protamine zinc insulin to another and, I think, in one instance have given it up and returned to a quick-acting insulin. A third disadvantage of protamine zinc insulin is its slow action which does not allow it to utilize the carbohydrate at breakfast even if that contains but one-fifth of the carbohydrate for the day. As mentioned, it was efficacious for 39 per cent of our patients, but in approximately one-half it was not. It is because of these three disadvantages of protamine zinc insulin that we welcomed the opportunity and felt deeply honored that the Eli Lilly Company and Burroughs Wellcome and Company invited us at the George F. Baker Clinic to test simultaneously, using the same standardized patients for a background, clear protamine zinc insulin, histone insulin and globin insulin. You will at once recognize, as did we, the high motives which actuated the action of these two manufacturing concerns and the standard thus set for other therapeutic investigations, and I trust the authorities in Washington will take cognizance of it.

This work has been carried out during the last nine months under the supervision of Alexander Marble and C. Cabell Bailey at the George F. Baker Clinic at the New England Deaconess Hospital. It would be wrong, even if there was the time, for me to give the details of their work, because it is their work and not mine, and although completed, not yet published. Naturally I have been conversant with it because it has gone on under my eyes, but it is to them and them alone that I am indebted for the privilege of calling your attention to certain conclusions which they reached and how they reached them. I hope you realize my obligation to the manufacturers of these new insulins, as well as to other recent investigators.

Experience gained by Marble in his study with Vartiainen of the

relative merits of regular and crystalline insulin in 1939⁹ was most helpful, and many of the methods then followed were employed. In general the conclusions of Marble and Bailey have been confirmatory of the reports hitherto published.

Three methods of procedure were adopted, first an intensive study of five volunteer patients, four males ages 19 to 32 years and one female age 47, to whom we all are greatly indebted. They remained in the hospital solely for the investigation for consecutive periods of 74 to 132 days. All had had diabetes for ten or more years, save one for 9.3 years. The diet for each patient was constant throughout, the carbohydrate ranging from 152 to 211 grams. The urine was tested qualitatively seven times daily and the sugar and nitrogen quantitated in the 24-hour quantity. Five blood sugar tests were made each day. Each type of insulin was employed from 7 to 32 days with each patient.

Two types of experiments were made with each of these five patients. Of these, the first was an estimation of the action of the special insulin under study during a day of fasting, begun with a subcutaneous injection of 0.15 to 0.2 unit per kilogram body weight, or 7 to 11 units. Upon these days blood sugar tests were made at 8 A.M. and half an hour later, and thereafter from 9 A.M. onwards hourly until midnight and again at 8 A.M. the following morning. In all, ten such fast days were made with histone zinc insulin, ten with globin zinc insulin, nine with clear protamine zinc insulin, six with crystalline insulin and four with turbid protamine zinc insulin, invariably using insulins of U-80 strength.

The other type of experiment with these five hospital patients was the observation of the effect of the various insulins over a period of days.

The second major plan of investigation was with twenty-one hospital patients upon whom the effect of the various insulins was watched over considerable periods.

The third group consisted of patients who continued, in their homes, the use of the various insulins which they had begun in hospital.

Histone insulin is insulin to which histone, a simple protein obtained from the thymus, is added. It was first described by Biasotti and co-workers,¹⁰ and later by Gray, Bischoff and Sansum,¹¹ and most recently by Barnes, Cuttle and Duncan,¹² who used a preparation made by the Eli Lilly Company to which zinc had been added. The last group obtained better results with it than with regular insulin or protamine zinc insulin. It was furnished us by the Eli Lilly Company. It is a turbid insulin

pH $7\pm$, the added protein is 3.2 mg. and the zinc content is 0.2 mg. per 100 units.

Globin insulin, first prepared by Reiner, Searle and Lang,¹³ consists of insulin to which a simple protein globin, made from red blood corpuscles of beef blood from which the iron containing fraction has been removed, is added. Its action was described to be more than twice that of regular insulin, giving results approximating or even better than protamine zinc insulin. It has been extensively studied and reported upon in publications by Bauman,¹⁴ and also by Andrews and Groat.¹⁵ It is a clear insulin, pH 3.7, the added protein is 3.75 mg. and the zinc 0.31 mg. per 100 units. This was furnished us through the kindness of Burroughs Wellcome and Company.

Clear protamine zinc insulin was also furnished us by the Eli Lilly Company, first, in fact, some four years ago. It has salmon sperm as the source of the protein, a pH of 3.3 — 3.5 and the added protein is 3.8 and the zinc 0.31 mg. per 100 units, and more glycerin than in turbid protamine zinc insulin.

A. Fasting Tests. Histone zinc insulin was given on two occasions each to five patients at 9 A.M. who had gone without food since the previous evening and who continued to fast for the following 23 hours. From the composite curve of the ten experiments it is evident that the effect began in half an hour, produced within two hours an initial fall of the blood sugar of 45 mg., possibly due to soluble insulin in the mixture, which continued with lessening force up to, at least, 15 hours, but with some effect still persisting at 24 hours.

Globin zinc insulin. The composite also of ten fasting day experiments showed that the effect began in one hour, the fall in blood sugar being rapid until the eighth to tenth hours and then more gradual until, at least, the fifteenth hour, followed by a slight but definite rise at 23 hours.

Clear protamine zinc insulin, like globin insulin, began to act in an hour, reaching the lowest blood sugar level in ten to eleven hours and then remained constant until the thirteenth hour and thereafter showed a definite rise up to the twenty-third hour.

For comparison I insert the curves for crystalline, turbid protamine zinc insulin and histone zinc insulin published by Barnes, Cuttle and Duncan.¹²

B. Maintenance Tests. A single dose of the respective insulin to be

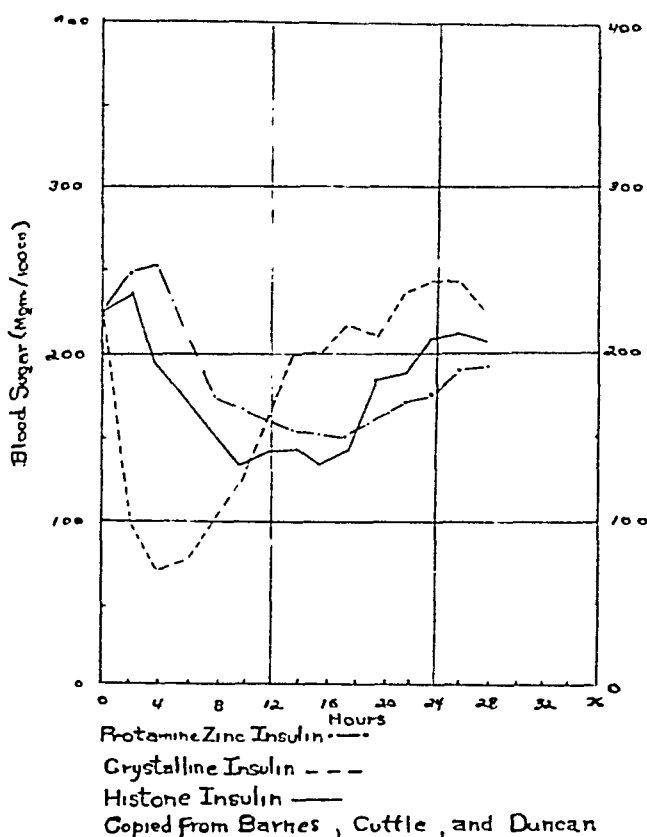


Chart 2

studied, often replacing two injections of crystalline and protamine zinc insulins, was given four of the five volunteer patients daily for 7 days and the customary 7 specimens of urine and 5 samples for blood sugar analyzed daily. Under less carefully controlled conditions other hospital patients were studied: nine with histone, seven with globin and a similar number with clear protamine zinc insulin.

Histone Zinc Insulin—Maintenance Tests. With this insulin the diabetes was well controlled. The fasting blood sugars were normal. There was a slight rise in blood sugar between 7 and 11 A.M., followed by a further rise between 11 A.M. and 2 P.M.; thereupon it fell until 5 P.M., rising again until 10 P.M. and then falling during the night. A bedtime lunch was given in all cases.

The maintenance tests with globin insulin indicated the need for three meals and an afternoon instead of a bedtime lunch. The fasting blood sugar values were usually normal. Between 7 and 11 A.M., the

blood sugar rose on the average 90 mg., between 11 and 2 it rose or fell slightly and between 2 and 5 it fell moderately (av. 27 mg.) or greatly (av. 140 mg.), depending upon whether a mid-afternoon lunch was given the patient, followed by a slight fall until 10 P.M. and the next morning usually a normal blood sugar.

In the maintenance tests with clear protamine zinc insulin, the fasting blood sugar was usually high, indicating a lack of sufficient action for 24 hours. The blood sugar rose between 7 and 11, which possibly might have been partly avoided if the insulin had been given at a longer interval before breakfast. It fell between 11 A.M. and 2 P.M. with an average fall of 38 mg. The fall between 2 and 5 P.M. depended upon whether a mid-afternoon lunch was given and was comparable to that of globin. The blood sugar remained constant between 5 and 10 P.M., tending to rise during the night. For good results an afternoon lunch was required, but a night lunch was not needed, and, indeed, was prejudicial to good effect. In general, regulation was difficult.

In maintenance tests with turbid protamine zinc insulin, the fasting blood sugars were always normal, an evening lunch usually being required. From 7 A.M. to 11 A.M. and 11 A.M. to 2 P.M., there was a continued rise of the blood sugar; thereupon a fall of an average of 67 mg. until 5 P.M. and a lesser fall in blood sugar up to 10 P.M.

C. Clinical Trials. With histone zinc insulin these resulted favorably with the seven cases tested, especially with the two children, 11 months and 2 years old respectively. The other five cases averaged 22 years of age. This favorable action is especially noteworthy, because the histone cases (barring the two infants) averaged 22 years of age as compared with the globin cases who averaged 41 years and the clear protamine zinc insulin cases who averaged 37 years. However, as much as I would like to do so, I must caution against drawing too favorable a conclusion from the excellent action of histone zinc insulin in replacing injections of both crystalline and protamine zinc insulin with the very young children 11 months and 2 years old respectively. Young children with diabetes of short duration often have low blood sugar values early in the day.

Globin zinc insulin worked still better in the clinical trials in the 21 hospital cases and in the patients' homes than with the five special study cases in the hospital. Provided an afternoon lunch was given, afternoon reactions were eliminated. One patient alone had a night re-

action, avoided later by a bedtime lunch. Globin insulin did not act favorably with one child of 21 months. Attention has been called to the average age of the globin patients being 41 years, thus conforming to the ideas of others who have worked with it, that it is especially of value with patients of middle age or older, i.e., with diabetes of moderate rather than extreme severity.

Clear protamine zinc insulin did not act as favorably in clinical trials as histone or globin insulin. The average age of the patients tested was 37 years. However, it should be said that four patients have been maintained upon it successfully since 1937.

CONCLUSIONS

For these I alone am responsible. If restricted to the use of a single insulin I would choose crystalline insulin, because it is the purest of all the types, is a clear insulin, acts promptly and therefore is indispensable in diabetic coma and can be given frequently enough and in sufficiently variable doses to control any type of diabetes throughout the twenty-four hours.

Next to it I would place protamine zinc insulin, because it acts so long that it is a constant protection for the patient against the vicissitudes of life. That one day's dose overlaps another for one or possibly two days is advantageous. Moreover, in about 40 per cent of the patients one daily dose before breakfast controls the disease and this percentage could probably be raised with careful adjustment of diet. Histone, globin and clear protamine zinc insulins have certain advantages over protamine zinc insulin, but not as yet sufficient to displace it.

Histone insulin combines to some extent the prompt action of crystalline with the prolonged action of protamine zinc insulin so that in an increasing number of cases one dose of it will replace the injection of crystalline insulin so often necessary to supplement protamine zinc insulin. It is possible it will serve in this way in very young children. Histone insulin causes few reactions and so far no allergic local phenomena have been reported. It has the fault of being a turbid insulin with the possibility of uneven distribution of the insulin precipitate, particularly in higher concentrations.

Globin zinc insulin is a clear insulin, produces so far as reported no allergic reactions, acts less promptly than crystalline and a little less promptly than histone insulin, but much more promptly than protamine

zinc insulin, and if an afternoon lunch is given, causes few reactions. Its effect lasts for about twenty-four hours.

Clear protamine zinc insulin is similar in action to globin insulin, but so far in our hands is not so uniform in action as globin insulin or as the other insulins.

In my opinion, a single dose of histone or globin insulin will control rather more diabetics than a single dose of protamine zinc insulin, but the difference is as yet so slight and the possibilities so good for overcoming the turbidity of histone insulin and the delayed action of both histone and globin, particularly globin, that it would seem definitely inadvisable to complicate the treatment of diabetes by introducing either upon the market in their present state. I think we have the right to expect that an insulin superior to protamine zinc insulin will be available to diabetics at some time in the future. In the meantime, both doctors and patients should more assiduously strive to control diabetes by better adjustments between exercise, diet and the excellent insulins now available.

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DIABETES IN PREGNANCY*

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BEFORE insulin was available conception was rare and when it did occur, there was a marked fatality in both mother and child.¹ Since the introduction of insulin the maternal hazards have diminished a great deal but the fetal mortality continues high. Measures are not exhausted that may lead to the solution of the present problem without recourse to risky or complicated procedures, that are much in vogue at the present time, such as cesarean section or endocrine therapy. Two possibilities that promise much have not received full consideration thus far in the management of pregnancy in diabetic women. These are: careful control of diabetes from the beginning of pregnancy and during its entire course, and, the effect of protamine zinc insulin in contrast to that of the unmodified, or regular insulin. When these two means of treatment will be completely worked up and applied, it may be that most, if not all, of the complications occurring in diabetes pregnancies will be set aside.

The relation of diabetes mellitus to pregnancy will be discussed under three headings:

1. Effect of pregnancy on carbohydrate metabolism.
2. Effect of diabetes upon the pregnant woman.
3. Effect of diabetes upon the fetus and the newborn infant.

EFFECT OF PREGNANCY ON CARBOHYDRATE METABOLISM

Renal glycosuria

A lowered renal threshold to the blood sugar commonly occurs during pregnancy. This consists of a leakage of sugar in the urine while the utilization of glucose within the body takes place in normal fashion. In itself, it is a harmless anomaly unless the glycosuria becomes intense, when through loss of large quantities of sugar it may induce acidosis

* Read January 22, 1941 in the series of Lectures in Obstetrics for Practitioners, at The New York Academy of Medicine.

and, consequently, give trouble. However, this is a very rare event and is one of the curiosities in medical or obstetrical practice. When renal glycosuria complicates a true diabetes, it may add serious difficulties in the control of the diabetes because of the loss of an exceedingly large amount of sugar in the urine. Under such circumstances the best has to be made of the situation and the blood sugar kept at as low a level as possible without causing hypoglycemic reactions. The aim in managing such a dilemma is that enough glucose will be metabolized to maintain normal nutrition regardless of the amount of sugar lost in the urine. This can usually be accomplished with careful supervision and regulation.

The differential diagnosis between renal glycosuria and diabetes may be somewhat difficult, but usually the existence of glycosuria while the blood sugar is at a level of 170 mg. per 100 cc. or less, justifies the diagnosis of renal glycosuria. Glucose tolerance tests may be misleading since in many cases diabetes and renal glycosuria co-exist. However, if the glucose tolerance is normal then the glycosuria may be taken to indicate that renal glycosuria alone is at fault and that diabetes is not present.

Onset of diabetes during pregnancy

This has been reported frequently. Williams² reports 9 women in whom the first symptoms of diabetes developed after conception; Herrick and Tillman³ found that in their 67 cases of diabetes complicating pregnancy, 15 began during pregnancy. Wilder⁴ notes that cases of true, severe diabetes arise in pregnancy. These and similar findings mean that the strain of pregnancy may change a latent diabetes into an active one.

Clinical course of diabetes in pregnancy

As a rule, there is an exacerbation of diabetes throughout pregnancy, that is, carbohydrate tolerance diminishes and insulin requirement increases. During labor the carbohydrate tolerance usually improves and the need for insulin is decidedly less. After delivery the diabetes generally ameliorates and returns to the state it was in before pregnancy began. These are the accepted generalities regarding the effects of pregnancy upon diabetes, but it is not safe to rely upon them for absolute guidance in the management of the individual case. Unpredictable variations in the severity of the diabetes do occur and may be of vital con-

sequence not only to the expectant mother but especially to the fetus. Therefore, it is worth making an analysis of reports on the clinical course of diabetes in the first, second and third trimesters, during labor, and after delivery.

First trimester. During this period carbohydrate tolerance is likely to be decreased according to Herrick and Tillman.³ A progressive decrease in carbohydrate tolerance during the entire pregnancy has been noted by Allen⁵ and by Hurwitz and Irving.⁶

Second trimester. During this period there is, as a rule, little change. In some cases there is an abrupt decrease in carbohydrate tolerance and a corresponding sudden increase in insulin requirement. This was noted in 3 cases by Herrick and Tillman³ and was found by Hurwitz and Irving⁶ at about the fifth month. These sudden shifts in the severity of the diabetes must be met promptly if harm shall not come to both mother and fetus. Consequently, Herrick and Tillman³ give the sound advice that during the second trimester the cases should be checked every 7 to 10 days.

Third trimester. Insulin requirements may diminish during the last trimester. The supposition is that the pancreas of the fetus supplies some insulin at this time, supplanting to a certain extent that furnished by the mother. On the other hand, Allen⁵ finds that carbohydrate tolerance diminishes during the third trimester. Herrick and Tillman³ state that marked changes in tolerance may be expected. Out of 20 patients, 9 gave evidence of very definite improvement in the diabetes status, 7 showed a decrease in carbohydrate tolerance, while 4 remained unchanged. A decline in tolerance over even a short period of time may result in the destruction of the fetus. Hurwitz and Irving⁶ observed one case which became sugar-free 10 days before term without insulin, after a previous requirement of 60 units per day. Consequently, the frequent checking of the diabetic pregnant woman and making suitable insulin and dietetic adjustments during the third trimester as well as during the second, is imperative.

Just before delivery. During labor an increased glucose tolerance is often noted. This may be due to increased activity of the voluntary muscles and to uterine contractions. On the other hand, an exacerbation of the diabetes and acidosis may develop and prove to be of serious significance to both mother and child.

Postpartum. The insulin requirement usually diminishes. According to

TABLE I

| | <i>Single</i> | | <i>Married and Widowed</i> | |
|--|---------------|---------------|--------------------------------|---------------|
| | <i>Male</i> | <i>Female</i> | <i>Male</i> | <i>Female</i> |
| Diabetes deaths, persons 45 years and over | 63 | 53 | 547 | 1,196 |
| Population, persons 45 years and over..... | 82,494 | 82,450 | 644,285 | 643,827 |
| Death rate per 100,000 | 76.3 | 64.3 | 84.9 | 185.7 |

New York City. Diabetes—Death and Death Rates—Older Adults, by Civil Condition.
Average 1931 and 1932. (Courtesy of Dr. C. B. Bolduan)

Diabetes deaths in persons 45 years and over are most frequent in married and widowed females, indicating that: *Pregnancy increases the liability to Diabetes.*

Allen⁵ this is the first time this occurs since the beginning of pregnancy.

The marked variations in carbohydrate tolerance, in the severity of the diabetes and in the insulin requirement, make it evident that careful control of the diabetes from the very beginning of pregnancy to its termination is necessary to prevent the disastrous effect such sudden changes in the carbohydrate metabolism may have upon both mother and fetus. Very few authors stress this fact. Herrick and Tillman³ insist on it and it may be that the good results they obtain in cases of diabetes in pregnancy, may be attributed largely to this method of controlling the diabetes.

The role of pregnancy in the production of diabetes in later life

The diabetes death rate, which really indicates the incidence of diabetes, is increasing more in females than in males. The increase is almost entirely in females over 45 years of age. It is interesting to note that diabetes deaths in persons over 45 years of age, occur at about the same rate in single males and females, whereas in the married and widowed, the death rate of females is far greater than that of males (Table 1). (The above data compiled by Dr. Charles F. Bolduan of the New York Department of Health have not been carried beyond the year 1932 because until the 1940 census figures are available, accurate rates can not be calculated.) From these facts it would appear that pregnancy increases the liability to diabetes. Joslin,⁷ in discussing these findings, stated that he observed that the average weight of his married

female patients above 45 years of age, was 181 lbs. as compared with a weight of 161 lbs. in single women. Consequently, he believes that the greater tendency to obesity of married females is responsible for the more frequent occurrence of diabetes in this group. Bolduan and I are still of the opinion that pregnancy is a predisposing factor in the development of diabetes after 45.

Acidosis

Acidosis is acknowledged as a common cause of fetal death in diabetes pregnancies (Herrick and Tillman;³ Wilder;⁴ Hurwitz and Irving⁶). Acidosis develops when the diabetes is neglected and is poorly controlled. The advisability of frequent checkups previously mentioned, becomes evident. It was also noted that the shift in carbohydrate tolerance may be sudden and that it has to be compensated for almost immediately if serious complications are to be prevented.

The case report of a 19 year-old diabetic primipara (Massachusetts Medical Society, Section of Obstetrics and Gynecology⁸) is worthy of note in this connection. This patient became unconscious because of acidosis after she went into labor, stillbirth followed, the mother survived. The report concludes: "Until diabetes in pregnancy can be controlled better than it is at present, any patient with severe diabetes who goes beyond 37 weeks with a viable child, stands a definite chance of losing the fetus by intrauterine death unless labor is induced or a cesarean section performed."

This drastic recommendation for induction of labor or cesarean section is based on insufficient grounds. If this patient had had adequate supervision by a doctor who understood the treatment of diabetes, coma should not have occurred and acidosis should have been remedied when it began, a number of hours at least, before "impending coma," let alone unconsciousness, developed. The institution of intensive treatment for diabetic acidosis, only when the patient became unconscious, is an admission that the diabetes was poorly supervised and the recommendation of routine cesarean section would seem a very radical remedy to forestall such a mishap. The mode of action suggested, i.e., that the diabetes specialist carry out frequent blood sugar estimations and prevent actual unconsciousness during labor, does not meet the aims of treatment in diabetes, nor does it fulfill the needs of the patient. Much more is required and it becomes evident that the attendance of a physician well

versed in handling diabetes, is necessary not only during labor, but throughout pregnancy.

Hyperglycemia

A high blood sugar in itself, without concurrent glycosuria, is, in all probability, of no significance,⁹ since under these circumstances, all the ingested sugar is metabolized and there is no loss in the urine and, as might be expected, there is no increased tendency to infection or other complication. On the other hand, if the glycosuria is marked, signifying the loss of a large amount of sugar to the body, then the results may well be disastrous. Under these circumstances, acidosis, protein destruction, loss of sodium and dehydration make themselves felt and, doubtlessly, have a serious effect upon the mother and often result in fetal death.

The use of protamine zinc insulin may modify the views we have held concerning the significance of glycosuria. This form of insulin results in adequate assimilation of sugar throughout the 24 hours in spite of the occurrence of glycosuria. In the treatment of non-pregnant diabetics, it is freely acknowledged that small amounts of sugar—10 to 20 grams per day—in the urine of diabetics are not harmful. Tolstoi and Weber¹⁰ have gone a good deal further than this and have claimed that the occurrence of large quantities of sugar in protamine zinc treated diabetics are of no consequence provided there is a liberal carbohydrate intake. Their case reports ring true but are so far removed from our previous conception of what adequate diabetes treatment consists of, that they have been accepted with some hesitancy until further proof is forthcoming. However, it must be remembered that for the first time a form of insulin is available that will regulate the carbohydrate metabolism throughout the entire 24 hours, resulting in both assimilation of glucose as glycogen, and the oxidation of glucose in spite of the existence of glycosuria.

Hypoglycemia

A blood sugar lower than normal, even to the point of inducing reactions, except just preceding and during labor, apparently is not harmful either to mother or fetus. In 14 patients with hypoglycemic manifestations, some reaching coma, anywhere from the second month of pregnancy to just before delivery, living babies were born in every instance (Herrick and Tillman³). Excessive doses of insulin just prior to

labor may result in hypoglycemia not only in the mother but also in the infant. This question will be discussed in a subsequent section.

EFFECT OF DIABETES ON THE PREGNANT WOMAN

Incidence of diabetes in pregnancy

The incidence of diabetes in pregnancy is not very great. This may be gathered from the statistics of the Municipal Hospitals in Greater New York which reveal that during the first six months of 1940 in a total of 8,598 pregnancies, there were 18 diabetic mothers, that is, 2.1 per thousand. For New York City the number of diabetic mothers is still lower, as shown by the reports of births and stillbirths to the Department of Health of New York City for 1939. During that year there were 83 diabetic mothers in 104,707 pregnancies, that is, 0.8 per thousand. The statistics on diabetes pregnancies from any one clinic are not conclusive, both because the reported cases are relatively few, and, furthermore, since the mode of dietetic management and insulin administration changes from time to time and any extensive series of diabetes pregnancies must be spread over a long period and the cases must thus be subject to considerable variation in treatment.

Infections of the urinary tract

According to Baldwin and Root,¹¹ infections of the urinary tract are more frequent, more protracted and of more serious outcome in the diabetic patient than in the non-diabetic. Whether or not this statement holds true in diabetics that are perfectly managed, that is, free from glycosuria, or are treated with protamine zinc insulin, remains to be proved though there is a good deal of evidence that hyperglycemia, in itself, does not favor the occurrence of infections. Hyperglycemia without glycosuria does not entail malnutrition of the tissues (protein destruction), dehydration (loss of sodium) or ketosis (incomplete oxidation of fatty acids). Consequently, bodily resistance is not diminished under those circumstances. It is possible that when protamine zinc insulin is used the same effects may be produced in spite of an existing glycosuria, though this observation of Tolstoi and Weber¹⁰ must be verified.

Infections of the urinary tract which cause cystitis, pyelitis or pyelonephritis may bring about the toxemias of pregnancy which, because of the urinary tract involvement, would be of the hypertensive or vas-

cular type that Herrick and Tillman³ claim is the most common form of toxemia of pregnancy in a diabetic.

Vitamin B₁ deficiency

Wilder⁴ lays considerable stress on the fact that requirements for vitamin B₁ are increased from three to five times in normal pregnancy, and when diabetes exists, there is still further need of B₁ above the usual normal necessity. Some of the toxemias of pregnancy, the hyperemesis of pregnancy, and the fetal oversize, have all been blamed on a relative deficiency of vitamin B₁. Wilder reports one case in which glycosuria, albuminuria, hemorrhagic retinitis with edema of the optic disc, subjective disturbance of vision, and mental cloudiness, were corrected by intensive administration of vitamin B₁, and he notes that similar results have been obtained in many other cases.

Hormonal therapy

Hormonal therapy, designed to correct a rising blood prolactin as carried out by Priscilla White¹² at the Deaconess Hospital in Boston, is, as I understand it, intended to check fetal mortality, whereas maternal risks are satisfactorily controlled by insulin and diet. This phase of the problem will therefore be considered in discussing the "Effect of diabetes upon the fetus."

Cesarean section

Cesarean section, carried out as a routine measure, has been advocated to insure a viable fetus. This subject will be discussed under the heading of "Effect of diabetes upon the fetus." However, the fact must not be lost sight of that cesarean section, regardless of diabetes, is much more dangerous to the mother than pelvic delivery and on that account deserves careful consideration before it is undertaken (Hurwitz and Irving⁶).

EFFECT OF DIABETES UPON THE FETUS AND THE NEWBORN INFANT

Age of mother

The age of the mother is an important factor in infant mortality. This may be noted from Table II, in which it is shown that the infant mortality increases distinctly after age 30. The age of diabetic mothers with stillbirths is higher than the age of non-diabetic mothers with still-

TABLE II

| <i>Age of Mother</i> | <i>Late Fetal and Neonatal Mortality</i> |
|----------------------|--|
| Under 20 | 25.1 per 1000 total births |
| 20 — 24 | 24.4 “ |
| 25 — 29 | 26.7 “ |
| 30 — 34 | 31.3 “ |
| 35 — 39 | 40.8 “ |
| 40 and over | 61.5 “ |
| For all mothers | 29.6 |

Late fetal and neonatal mortality (full term births). Statistics from upstate New York—1936. *Age of mother an important factor in infant mortality.*

Ages of diabetic mothers with stillbirths considerably higher than those of non-diabetic mothers with stillbirths. Diabetic mothers 50 per cent are 35 years or older; non-diabetic mothers 23 per cent are 35 years or older. *Age of diabetic mothers with stillbirths greater than age of non-diabetic mothers with stillbirths.*

births. (Diabetic mothers 50 per cent are 35 years or older; non-diabetic mothers 23 per cent are 35 years or older). Consequently, it may be concluded that the older age of the mother is a factor in the greater tendency to late fetal mortality which is characteristic of diabetes.

Control of diabetes

The effects of poorly controlled diabetes and the significance of acidosis, hyper-, and hypoglycemia have been discussed in the section on the “Effect of pregnancy on carbohydrate metabolism.” It suffices at this point to stress the dangers of acidosis both to the fetus and the mother. Hurwitz and Irving⁶ claim from their experience as well as from a study of the literature, that the most frequent cause of fetal death is neglect of the diabetes, with resultant acidosis. Maceration of the fetus is regarded as the complication of an uncontrolled diabetes (Potter and Adair¹³).

Overweight of the fetus

Fetal overweight has always been considered as a major hazard in diabetes pregnancies. The opinion appears to be growing that it occurs only when the diabetes of the mother has not been properly regulated (Potter and Adair¹³). Herrick and Tillman,³ who stress the importance of control of diabetes throughout the entire pregnancy, state that among

the viable births the child of a diabetic mother is as likely to be underweight as overweight. Wilder⁴ claims that he has not encountered large babies, possibly because in earlier cases, low carbohydrate diets were used, and recently, because the child had been delivered by cesarean section between the 36th and 37th week. Another possible explanation that Wilder puts forward has been his insistence on a diet richly supplied with vitamins and calcium, since it is not improbable that a relative lack of vitamin B₁ is responsible for an oversize fetus.

Overweight is due to an extensive accumulation of fat and not to skeletal changes.

It has been suggested that disturbances in pituitary activity, supposed to occur in diabetes, are responsible for the overweight.

The significance of all these claims and statements is not perfectly clear but one cannot help gaining the impression in reading from the various reports that as Potter and Adair put it: "If the patient's urine has been kept relatively sugar-free by diet and insulin, and acidosis has not occurred, a live-born infant within normal limits of size, will probably be delivered naturally."

Hormonal imbalance

Priscilla White and her co-workers for a long time have been furnishing evidence that accidents commonly seen in diabetes pregnancies are not due to imperfectly controlled diabetes but to an abnormal hormone balance. White and Hunt¹² in a recent publication summarize their point of view and their results as follows: "Our present conception of the mechanism of the accidents in diabetic pregnancies has been the outcome, first, of our realization that adequate dietary control of diabetes and insulin therapy did not lower the fetal mortality rate and, second, our correlation of the behavior of diabetic pregnancies in relation to the balance of pregnancy hormones—chorionic gonadotropin, estrogen and progesterone. We believe (1) that an abnormal rise of chorionic gonadotropin after the twentieth week to a level of 200 rat units per hundred cubic centimeters of blood predicts in the diabetic premature delivery, stillbirth and neonatal deaths, (2) that these accidents are caused by a failure of production or of metabolism of estrogen and progesterone and (3) that they are prevented by continuous substitutional estrogen and progesterone therapy in replacement doses."

Cesarean section

There are two schools of thought:—those who, like Wilder,⁴ believe in early cesarean section in every diabetes pregnancy, and those who believe as do Herrick and Tillman³ that cesarean section should be reserved for those cases in which there is a supporting obstetric indication. According to others there are special indications for cesarean section such as, the hormonal imbalance as sponsored by Priscilla White, or the excessive size of the fetus. In general, the trend seems to be toward a conservative attitude and the results reported by various authors when the diabetes has been controlled from the start, showed figures which are decidedly encouraging and comparable to those offered by the advocates of frequent recourse to cesarean section.

Hypoglycemia of the newborn

Wilder⁴ claims that the usual cause of neonatal deaths is hypoglycemia as evidenced by the occurrence of convulsions and that this can be controlled by glucose injections. On the other hand, there are many (Miller and Ross,¹⁴ Sisson,¹⁵ and others^{16, 17}) who are unable to confirm this finding.

In Sisson's¹⁵ series of 65 infants born of diabetic mothers, a high blood sugar was the rule and hypoglycemia was a rare complication. A low blood sugar when it did occur was ascribed to insulin given to the mother just before delivery. The restriction of insulin to the minimum necessary for control of the diabetes just prior to delivery would therefore be clearly indicated. Consequently, the routine procedure of glucose injections directly after birth is useless and should not be carried out unless the actual blood sugar determination shows a hypoglycemia.

Hypoglycemia in the mother does not necessarily indicate that the infant will suffer on this account. Herrick and Tillman³ note that in two patients with hypoglycemia while in labor, the fetal blood taken at the same time showed an extremely low level of sugar. Clinically, however, these infants behaved normally and gave no evidence of hypoglycemia.

Asphyxia of the infant

Asphyxia has been stressed as a frequent cause of neonatal death. Sisson¹⁵ states that there seems to be a rather typical symptom complex. It usually occurs in the first 12 hours of life and is associated with fre-

quent and labored respirations. Physical examination shows unexpanded lungs. All reflexes are suppressed but muscular contractions of the face and extremities are common. The condition suggests an intrauterine disturbance with involvement of the respiratory center. In many instances the precipitating cause has seemed to be the insufflation of amniotic sac contents. This occurred most frequently with infants delivered before the eighth month. Wilder⁴ describes the treatment of this condition as follows: "Following the delivery of the child, efforts are directed immediately to prevent hypoglycemia and to combat asphyxia. Care is taken to be certain that the pharynx and trachea are free of mucus and amniotic fluid, by keeping the head dependent and, if necessary, by aspirating with a tracheal catheter. Occasionally inhalation of carbon dioxide and oxygen is needed to establish respiration. When the baby is breathing it is placed in a Hess incubator equipped with a cover and connected with an oxygen tank. Flow of oxygen is regulated in order to maintain an oxygen concentration of 40 to 50 per cent for the first few hours. The concentration of oxygen in the incubator gradually is diminished and when the color of the infant remains normal in the ordinary atmosphere, administration of oxygen is discontinued."

SUMMARY AND CONCLUSIONS

Pregnancy accentuates an existing diabetes.

Pregnancy favors the development of diabetes in later years.

The older age of diabetic mothers is an unavoidable predisposing factor to stillbirths.

Large amounts of Vitamin B₁ are required during pregnancy and particularly when diabetes exists. According to Wilder many of the complications of diabetes pregnancies may be set aside by suitable doses of B₁.

The impression is growing that asphyxia of the infants of diabetic mothers is a frequent cause of neonatal death.

The opinion is expressed with increasing frequency that routine cesarean section is unnecessary in diabetes pregnancies and that equally good results are obtained when cesarean section is performed only when there is an obstetric complication that would be regarded as an indication for cesarean section in non-diabetes pregnancies.

It is possible and would appear to be probable that regulation of the diabetes (meaning adequate deposit of glycogen in the tissues, ample

oxidation of glucose and freedom from acidosis) from the very beginning to the termination of pregnancy in a diabetic woman will do away with all the complications of pregnancy to which mother and fetus are liable. This includes oversize, maceration and other fetal hazards. The diabetes should not only be well controlled from day to day but care should be taken that the body's carbohydrate metabolism is proceeding along normal paths and providing proper utilization of glucose every hour of the day and night. This is stressed because with protamine zinc insulin we now have an agent which furnishes perfect adjustment of glucose assimilation continuously for more than 24 hours and has distinct advantages over the first, unmodified insulin which acted for only 4 hours after each injection and failed to prevent a resumption of the diabetic state after its period of influence had ceased. It would seem possible that all the problems of pregnancies in diabetic subjects may be solved by complete control of the carbohydrate metabolism from the very beginning of pregnancy to the termination of labor, and for the accomplishment of this end protamine zinc insulin should prove to be of inestimable help.

Sudden and marked variations in the severity of the diabetes may occur in the course of pregnancy, especially during the second and third trimesters. Such changes may call for either more or less insulin. If these demands are not met, serious consequences are in store for both mother and child. Therefore, during the second and third trimesters the diabetes should be regulated every 7 to 10 days.

During labor the most meticulous care should be taken to check acidosis and to prevent hypoglycemia in the mother. All authors are agreed on the point that acidosis is a very serious complication and because of its fulminating progress must be regarded as an emergency. The occurrence of the dangerous hypoglycemia in the newborn apparently can be prevented by keeping the insulin administration to the prospective mother within reasonable limits, as governed by blood sugar determinations.

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PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

JANUARY 8—*The New York Academy of Medicine. Annual Meeting.* Executive session—a] Reading of the Minutes; b] Amendment to By-Laws; c] Presentation of diplomas. ¶ Presentation of annual reports (to be read by title): The Council, The Trustees, The Treasurer, Committees. ¶ Papers of the evening, *Program under the joint sponsorship of The New York Academy of Medicine and its Section of Surgery and The New York Surgical Society*—War Wounds— a] Determining factors in the end-results following war wounds and compound fractures, H. Winnett Orr, Chief Surgeon, Nebraska Orthopedic Hospital; b] The treatment of head injuries, James C. White, Assistant Professor of Surgery, Harvard Medical School. ¶ Report of election of fellows.

JANUARY 15—*The Harvey Society in affiliation with The New York Academy of Medicine.* The fourth Harvey lecture, "Intermediary Metabolism in Diabetes Mellitus," William C. Stadie, Professor of Research Medicine, University of Pennsylvania.

SECTION MEETINGS

JANUARY 6—*Dermatology and Syphilology.* Presentation of cases—a] Presbyterian Hospital; b] Vanderbilt Clinic. ¶ Discussion. ¶ Executive session.

JANUARY 6—*Combined Meeting Section of Neurology and Psychiatry and the New York Neurological Society.*—a] Reading of the minutes; b] Case presentation. Neurosis of seventy-years' standing, C. P. Oberndorf, Arnold Eisendorfer. ¶ Papers of the evening—a] Spastic and flaccid hemiplegia of cerebral origin, Ben H. Balser; Discussion, Tracy J. Putnam, Margaret A. Kennard; b] Vis-

ualization of the brain and spinal cord with diiodotyrosine gelatine contrast media including later observations, Harold H. Leff, J. Arthur MacLean; Discussion, Tracy J. Putnam, Leo M. Davidoff.

JANUARY 8—*Combined Meeting Section of Historical and Cultural Medicine and the Section of Pediatrics.* ¶ Papers of the evening—a] The throat distemper of 1735-1740, Ernest Caulfield (by invitation); b] The evolution of our present knowledge of hypersensitiveness, Bret Ratner; Discussion, Ulrich Friedemann (by invitation), Bela Schick.

JANUARY 19—*Ophthalmology.* ¶ Instruction hour 7:00 to 8:00 o'clock. Visual pathways—A clinical review, Ferdinand Koch (by invitation). ¶ Exhibit—Exophthalmos, A. D. Ruedemann, Cleveland (by invitation). ¶ Executive session. Reading of the minutes. ¶ Presentation of cases—a] A case of molluscum contagiosum of the lid margin with pannus, Clement McCulloch (by invitation); b] A case of tuberous sclerosis, Murray Last. ¶ Papers of the evening—a] Heparin treatment of thrombosis of the central retinal vein, Marion Cuthbert (by invitation); b] The clinical and surgical aspects of pituitary tumors, Leo M. Davidoff; c] The roentgenological aspects of pituitary tumors, Cornelius G. Dyke; Discussion, Foster Kennedy.

JANUARY 20—*Joint Scientific Session Section of Medicine and the New York Heart Association, Heart Committee of the New York Tuberculosis and Health Association.* Annual report of the New York Heart Association, Ernst P. Boas. ¶ Papers of the evening—a] Experimental and clinical studies in the use of anti-coagulants in cardiovascular disease with special reference to heparin and dicoumarin, Andrew G. Prandoni (by invitation), Department of Internal

Medicine, New York Post-Graduate Medical School & Hospital, Columbia University; Discussion, Irving S. Wright; b] Some chemical changes in the myocardium accompanying heart failure, Victor C. Myers (by invitation), Professor of Biochemistry, Western Reserve University, Cleveland, Ohio; Discussion, Maurice Bruger (by invitation).

JANUARY 21—*Genito-Urinary Surgery*. Reading of the minutes. ¶ Papers of the evening—a] Studies on the etiology of Hunner ulcer, Edward Cathcart, Detroit (by invitation); b] Bladder complications following operations for advanced rectal carcinoma—a new operative device, Benjamin Barringer; c] The treatment of neurogenic urinary incontinence with trasentin. Studies in bladder function (lantern slides), Irving Simons; Discussion, J. Sturdivant Read.

JANUARY 21—*Otolaryngology*. Reading of the minutes. ¶ Presentation of cases—a] Lipoid proteosis, Marion B. Sulzberger; Discussion, Julius F. Neuberger (by invitation). ¶ Papers of the evening—a] Histamine in the treatment of nasal allergy, Laurence Farmer; Discussion, Arthur J. Cracovaner; b] Experiences in the treatment of Ménière's syndrome, Miles Atkinson (by invitation); Discussion, Foster Kennedy. ¶ General discussion. ¶ Executive session.

JANUARY—*Orthopedic Surgery*. No meeting of the Section was held in January because of the annual meeting of the American Academy of Orthopaedic Surgeons in Atlantic City, January 11-15.

JANUARY 27—*Obstetrics and Gynecology*. Program presented by the Woman's Hospital. ¶ Executive session, reading of the minutes. ¶ Papers of the evening—a] Uterine prolapse, its management and surgical treatment, Ralph A. Hurd; b] Carcinoma of the corpus uteri, Diagnosis and treatment, George Gray Ward; c] Caesarean section, Advantages and disadvantages of the various surgical techniques, James P. Marr; d] Maternal mortality, A consideration of common errors in the conduct of labor and delivery, Ralph L. Barrett, Chairman Special Committee on Maternal Welfare, New York County Medical Society. ¶ General discussion.

AFFILIATED SOCIETIES

JANUARY 22—*New York Pathological Society in affiliation with The New York Academy of Medicine*. ¶ Papers of the evening — Iso-immunization and the pathogenesis of erythroblastosis fetalis: a] The pathogenesis of erythroblastosis fetalis, Philip Levine (by invitation); b] The pathological aspects of erythroblastosis fetalis, S. H. Polayes; c] The clinical and hematological aspects of erythroblastosis fetalis, Peter Vogel (by invitation); d] Iso-immunization and the prevention of intra-group transfusion accidents, E. M. Katzin (by invitation). ¶ Executive session, election of officers.

JANUARY—*New York Roentgen Society*. The regular monthly meeting of the Society was omitted in January, because of the Annual Mid-winter Eastern Conference of Radiologists, which was held January 23 and 24 at the Hotel Biltmore, New York.

DEATHS OF FELLOWS

FOSTER, ALLYN KING, JR.: 136 East 57 Street, New York City; born in Cornwall, Connecticut, March 8, 1905; died in New York City, January 17, 1942; graduated in medicine from Rush Medical College, University of Chicago, in 1929; elected a Fellow of the Academy January 7, 1937.

Dr. Foster had served his internship at St. Luke's Hospital and was junior assistant surgeon to the Post-Graduate Hospital, assistant surgeon to the Downtown Hospital, assistant surgeon to the O.P.D. at Post-Graduate Hospital and clinical assistant surgeon to the O.P.D. of the Lincoln Hospital. He was a Fellow of the American Medical Association and a member of the State and County Medical Societies.

FURNISS, HENRY DAWSON: 54 East 62 Street, New York City; born in Selma, Alabama, March 25, 1878; died in New York City, January 25, 1942; graduated in medicine from the Medical Department of the University of Virginia in 1899; elected a Fellow of the Academy March 7, 1907.

Dr. Furniss was professor of obstetrics and gynecology at the New York Medical College and attending obstetrician and gynecologist to the Flower and Fifth Avenue Hospitals; visiting surgeon to the Metropolitan Hospital; consulting gynecologist to the New York Post-Graduate Hospital, Broad Street Hospital, New Rochelle Hospital, St. Luke's Hospital at Newburgh, Holy Name Hospital at Teaneck, Hackensack Hospital of New Jersey, All Soul's Memorial Hospital at Morristown, and consulting cystoscopist to the New York Infirmary for Women and Children. From 1917 to 1927, Dr. Furniss was professor of gynecology at the New York Post-Graduate Medical School, having joined that faculty in 1904 as instructor of gynecology.

Dr. Furniss was a diplomate of the American Board of Urology, a diplomate of the

American Board of Obstetrics and Gynecology, a Fellow of the American Medical Association, a Fellow of the American College of Surgeons, a member of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, the Southern Surgical Society, the American Urological Association, and the State and County Medical Societies.

GOODFRIEND, NATHAN: 44 West 77 Street, New York City; born in Galsech, Austria-Hungary, June 18, 1880; died in New York City, January 17, 1942; graduated in medicine from the College of Physicians and Surgeons in 1902; elected a Fellow of the Academy April 3, 1913.

Dr. Goodfriend was attending ophthalmologist to the Bronx Hospital and secretary of its medical board; and assistant surgeon to the Manhattan Eye, Ear and Throat Hospital. He was a Fellow of the American Medical Association, a Fellow of the American College of Surgeons and a member of the State and County Medical Societies.

LOUGHRAN, ROBERT LIVINGSTON: Sharon, Connecticut; born in Kingston, New York, March 28, 1873; died in Sharon, January 27, 1942; received the degree of A.B. from Princeton University in 1895; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1899; elected a Fellow of the Academy May 18, 1905.

Dr. Loughran was at one time professor of otology and attending otologist to the New York Post-Graduate Medical School and Hospital. He was a diplomate of the American Board of Otolaryngology, a Fellow of the American College of Surgeons, a member of the American Laryngological, Rhinological and Otological Society and its secretary from 1924 to 1936, and a member of the American Medical Association and the State and County Medical Societies.

In the first world war, Dr. Loughran held the rank of Major in the Army Medical Corps. He served as superintendent of the Ancon Hospital and as Chief Public Health Officer of the Panama Canal Zone from 1917 to 1919.

TAYLOR, ALFRED SIMPSON: 116 East 68 Street, New York City; born in Manchester, Connecticut, January 17, 1868; died in New York City, January 16, 1942; received from Brown University the degrees of Ph.B. in 1891 and A.M. in 1892; graduated in medicine from the College of Physicians and Surgeons in 1895; elected a Fellow of the Academy February 4, 1904.

Dr. Taylor was professor of clinical surgery of the neurological department at Cornell University Medical College from 1910 to 1930. He was consulting surgeon to the Memorial, Fordham and New York Hospitals; and consulting neurosurgeon to the New York Neurological Institute and St. Luke's, General Memorial and Tarrytown Hospitals. He was a Fellow of the American Medical Association and the American College of Surgeons; and a member of the American Surgical Society, the Society of Neurological Surgeons, the American Neurological Association and the County and State Medical Societies.

Dr. Taylor contributed many papers in the field of general and neurosurgery and developed a method for the reduction of dislocations of the spine.

WALDIE, THOMAS EDWARD, 1215 Madison Avenue, New York City; born in Brooklyn, November 20, 1884; died in New York City, September 18, 1941; graduated in medicine from Cornell University Medical School in

1907; elected a Fellow of the Academy, January 6, 1927.

Dr. Waldie was a member of the State and County Medical Societies, and the American Medical Association. He was Pediatrician to St. Vincent's, St. Clares, Willard Parker and the New York Foundling Hospitals, and Director of the Department of Pediatrics of the Misericordia Hospital.

WOLFF, JULIUS: 1112 Park Avenue, New York City; born in New York City, December 3, 1869; died in New York City, January 26, 1942; received the degree of A.B. from Harvard University in 1890; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1893; elected a Fellow of the Academy May 4, 1899.

Dr. Wolff was ophthalmologist to Randall's Island Hospital, 1899-1905; and assistant ophthalmic surgeon to Bellevue Hospital, 1927-32. In 1907 he became associated with The Mount Sinai Hospital as assistant adjunct attending surgeon; from 1923 to 1932 he was attending ophthalmic surgeon and head of the department of ophthalmology; and from 1932 until the time of his death, he was consulting ophthalmologist to that institution. He was a diplomate of the American Board of Ophthalmology, a Fellow of the American Medical Association, and a member of the State and County Medical Societies.

BULLETIN OF THE NEW YORK
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BULLETIN OF
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OF MEDICINE



APRIL 1942

DETERMINING FACTORS IN THE
END-RESULTS FOLLOWING WAR
WOUNDS AND COMPOUND FRACTURES*

H. WINNETT ORR

Chief Surgeon, Nebraska Orthopedic Hospital, Lincoln, Nebraska

THERE was a short period in the history of surgery when we could be and were quite definite about our attitude toward compound fractures and compound fracture wounds. We did not treat the wound. The wound dressing was designed only to exclude infection. Unfortunately, this period was very short. I refer to the time about 1865 to 1870 when the true Lister method was proposed, described and employed by Joseph Lister himself.

In discussing wounds and compound fractures this evening, I shall first remind you that in order to deal successfully with this problem we must return, not to the technique or to the exact method of Lister, but to the Lister point of view. This original conception was described perfectly by Lister and was really comprehended by many of his pupils and contemporaries. Even a few of his successors were able to maintain the original Lister attitude toward wound infection. Generally speaking, those surgeons who adhered to the Lister ideal were few, while those who departed on various paths and in many directions were many.

* Read January 8, 1942 at the Annual Meeting of The New York Academy of Medicine.

As an illustration, I may quote from Dr. James L. Little (in 1877), lecturer on operative surgery and surgical dressings in the College of Physicians and Surgeons, New York:*

"We will turn our attention this morning to the subject of antiseptic surgery, a topic at present of universal interest and one with which, even should you never practice it, scientific medicine demands that you should be familiar. Professor Lister, accepting the germ theory, has applied to the treatment of open wounds an entirely new method which has so far yielded the most wonderful results. The principle of Lister's method is essentially this: In treating an open wound let neither the air, the instruments you use, your hands or the dressings that are to be applied, nor in fact anything come in contact with the wound unless it has been thoroughly saturated or wet with a solution of carbolic acid, and at the same time keep the wound thoroughly drained."

This was *not the principle* of the Lister method, only some of the details of the Lister technique from which Dr. Little and many others promptly departed.

Dr. Little continued: "Carbolic acid comes in crystals, but the addition of a little water dissolves them. You should procure two bottles; one that will hold a quart and one that will hold two quarts, and a two-ounce graduate. To 30 ounces of water add an ounce and a half of the carbolic acid and you have a solution of the strength of one part of carbolic to twenty of water. From the two quart bottle pour off four ounces and add the same amount of carbolic acid. You then have a solution of one part of carbolic acid to forty of water. Now you are ready to employ the Lister method so far as the solutions are concerned."(!)

Dr. Little described at the same time, the use of thymol which had been employed not very successfully by Dr. Weir. Dr. Little expressed the hope, however: "That some more pleasant antiseptic will soon be discovered to take the place of the disagreeable carbolic acid."

Dr. Little employed the spray and described its use in great detail. Then he said: "We will now turn our attention to the antiseptic gauze. This is made of very coarse muslin or cotton gauze sprinkled with a hot mixture of resin and paraffin and one part of crystallized carbolic acid. Another material which can be prepared in the same way or pur-

* From a *Series of Clinical Lectures*, Edited by E. C. Seguin, Vol. III, No. xi, p. 298. New York, G. P. Putnam & Sons, 1878.

chased from a dealer, is the mackintosh cloth or protective oiled silk."

Lister taught that a certain kind of safety pin should be employed with a guard protecting the point of the pin. He said that even a pin hole through the mackintosh might permit the entrance to the wound of enough germs to cause the death of the patient.

In 1877, however, both Lister and Dr. Little were advocating the use of rubber drainage tubes. These tubes damaged the wound surface and permitted the access of new infection to the deep recesses of the wound.

These inconsistencies—exposure for dressings with damage to the wound surface, and the drainage tube opportunity for infection, have led to many of our difficulties in the control of fractures and in the protection of the wound against secondary infection. They have led to pyemic and septicemic complications and have predisposed to inflammation, scar formation, disability and deformity.

In 1904 when I began the study of orthopedic surgery I was drilled by Dr. Ridlon in the teachings of Hugh Owen Thomas (even with regard to intestinal obstruction) but he never did ask me to read the writings of Lister. I had not read all of them until after the war of 1917-1918. It had been my impression that Lister's original writings were very much out of date. I was familiar with the fact that Lister had renounced the antiseptic method as far as the carbolic spray was concerned. I thought then, as I have found many other surgeons to think, that Lister had abandoned his original conception of antiseptis when he abandoned the spray.

As I re-read the writings of Lister in 1919, I found that he had, to an extent, receded from his original teaching as to the exclusion of infection. He did allow himself to be influenced by his colleagues and his contemporaries to begin the search for a less offensive chemical than carbolic acid and for one which might actually cure wound infection.

But while Lister had been led by Robert Koch and others to try mercurial antiseptics, he regretted a tendency toward careless chemical dressings as a substitute for exclusion. Chemical wound dressings and chemotherapy were not then and have never been the true Lister method.

It is this search for a chemical that will kill germs without harm to the patient that has done antiseptic and aseptic surgery much harm. For example, a British surgeon said in 1918: "In dealing with compound

fractures and compound fracture wounds it is important for the surgeon not only to defend against infection, but to know when to attack." But what many of us forgot in those days was that in attacking the infection we were often attacking the patient as well, and about the time that the infection and the germs were in retreat, the patient was about ready to surrender also.

We have all been misled, as Lister was, by the recovery of patients for whom certain kinds of antiseptic gauze or certain forms of chemical solutions were employed. We lose sight of the point that before the days of Listerism and in spite of some of the revolting wound treatments that were then employed, patients got well in spite, rather than because of the surgeon's efforts.

Many of our correct ideals with regard to treatment of wounds and fractures were inherited from Hunter, Hilton and Hugh Owen Thomas. In a period in New York surgery fifty years ago tuberculosis of the hip or morbus coxarius was being treated by machines or apparatus designed to provide immobilization and traction for the hip. After many years of travail, during which the Sayre, Washburn, Stephen Smith, Hutchinson, Bauer, Shaffer, Duncan Eve, Wyeth, Stillman and Roberts splints were devised, manufactured and applied, we came to the point where real immobilization and rest were obtained by the Thomas splint, much simpler, lighter in weight, more efficient and less expensive; or by the plaster-of-paris cast. During those days we had advocates of radical surgery, motion, ambulation, and even chemotherapy for tuberculous joints—but no more.

We know that rest rather than radical surgery or medication will assist patients to recover from tuberculous bone and joint disease.

But we have not made so much progress in the matter of compound fractures. There have been too many attempts to individualize therapeutic technique and apparatus for different patients, different occasions and especially for different splints and surgeons to arrive at standard methods, continuity, or systematic treatment.

A common admonition of surgeon-teachers is that the surgeon on the spot in an emergency must decide the special apparatus, methods, and program appropriate for any patient. Every surgeon should have in mind that certain fundamentals, such as, restoration to normal position, immobilization, control of hemorrhage, and protection against further trauma and infection are essential and should always come first.

In acute infections even more than in chronic bone and joint disease, immobilization and rest are necessary to avoid or reduce inflammation, scarring and subsequent fixation, adhesions and ankylosis.

We do not seem to have arrived at this "rest" point of view for the acutely inflamed fractures and compound fracture wounds. There is still the attempt to diminish the amount of apparatus, to provide more joints and mobility, to make our patients ambulatory and to render less efficient rather than more so the kind of control which Thomas described long ago as rest "enforced, uninterrupted and prolonged."

We should not forget that scarring, stiffness and disability in the vicinity of fractures are brought about by improper motion, inflammation and irritation just as they are in tuberculous joint disease.

When I began my infrequent-dressing and rest method for osteomyelitis, infected wounds and compound fractures about twenty years ago, I had become convinced that the Carrel-Dakin, Willems, and Blake teachings, and primary and secondary suture were all doing much harm. My feeling arose partly out of realization that the teachings of Lister, Hilton, Hugh Owen Thomas and Ridlon regarding infection and rest were being violated. I believed firmly *that wound surfaces should be protected, that infected wounds of any degree should be drained, that all fractures should be reduced and immobilized, and that any injured or inflamed limbs should be protected against muscle spasm and other painful movements.*

A very few clinical trials were sufficient to convince me of the correctness of these assumptions. Many years of further clinical experience have assured me that these fundamentals are correct but that other details of treatment are often incidental and unnecessary.

My own results have been obtained without sutures, without drainage tubes and without antiseptic wound dressings. Sometimes cures or results attributed to chemical agents or "modified" techniques have been attributed wrongly to them, when better immobilization, rest and protective methods have given the patient his own chance to recover.

I could quote many reports from recent literature to illustrate this point. Perhaps one from a New York surgeon will be sufficient. In *Bone and Joint Surgery* for October, 1941, he says: "I have recently treated 45 fractures of the tibia by open operation. The results in all 45 cases have been good, though recovery in one or two was somewhat delayed. To date there has been no loss of life or limb attributable to

the open method despite the fact that as yet none of the newer drugs, such as sulfanilamide has been used as a prophylactic against infection." I am not quite sure whether this New York surgeon is being naive—a term sometimes reserved for those of us from the provinces—or whether he is "pulling our leg."

In this connection we might do well to recall what Dr. Flexner said in his book on "Medical Education": "There is a wide-spread impression that the scientific quality of medical practice is dependent upon the part played by the laboratory. This is not the case." Clinicians especially are inclined to regard the laboratory worker as always scientific and more or less infallible. It should be remembered, I think, that mistakes as to cause and effect, so often attributed to the clinician, may be made by the laboratory worker too, especially if he tries to carry his methods and conclusions into the field of practice.

It is interesting that in recent months a piece of research has been carried out which has had the effect of rationalizing completely all of our contentions regarding the importance of immobilization and rest in the treatment of inflammation and infection. This work was done, in part, by Dr. Trueta who made such a fine contribution to the plaster-of-paris cast and infrequent-dressing method by his work in Barcelona during the Spanish War. Dr. Trueta has recently been at Oxford, England, and has conducted a study with Dr. Barnes of Oxford on the influence of immobilization upon the lymphatic circulation in the extremities.

Barnes and Trueta published in the *Lancet*, London, May 17, 1941, page 263, an article on the absorption of various toxins and other materials from the mesenchymal tissues under circumstances similar to those in wounds and compound fractures.

Barnes and Trueta tied off the lymphatic circulation in animal limbs and introduced certain organisms into the tissues. They found that with the lymphatics obstructed, very few of these organisms got into the blood or into the spleen. Also, even from recent wounds, very few organisms were taken up by the freshly injured blood vessels, but such as were carried into the body of the animal at all, were taken by way of the lymphatics.

Snake venoms, some of which were so poisonous that they would kill animals in ordinary ways within ten minutes, could be excluded from the body of the animal generally by obstruction of the lymphatic circulation in the poisoned extremity. As soon as the ligated lymphatics

were relieved, however, even after an hour or so, the poison which had been held in the extremity by this ligature, escaped into the body and the animals promptly died.

Another experiment had to do with the reduction of the lymph flow by physiologic means. Rabbits had their lower extremities completely immobilized by means of plaster-of-paris double spica casts. Then snake venom was injected into the immobilized lower extremity, and one animal was found to be perfectly well after 105 minutes; then the plaster was removed and the animal allowed to move the limb about and died within seven minutes. A second animal remained in plaster for 210 minutes and died 60 minutes after the removal of the cast.

One method by which edema may be prevented, Dr. Trueta says, is by the enclosure of the injured parts in a plaster cast. The reduction of the lymph flow obtained by this means is further enhanced *if local drainage of the inflamed parts is provided by incision.*

The support adduced, by Dr. Trueta's research, for the immobilization and skeletal fixation of these extremities in plaster-of-paris is of the greatest importance. It has an important bearing on the immobilization and rest treatment of all infected wounds and fractures. It not only explains the excellent results we have obtained by this method, but points the way to further study along this line.*

I wish to refer briefly to the report of the Committee on Fractures and other Traumas published in *Surgery, Gynecology and Obstetrics*, November, 1941. This resolution was adopted at New Orleans last January. The conclusions of this Committee may be summarized as follows:

1. The use of snug-fitting plaster encasements in initial treatment of acute compound fractures is inadvisable.
2. Early splinting, utilizing fixed traction, should be followed by adequate debridement at the earliest possible time.
3. Wounds of the soft parts, not involving bones, joints, nerves or tendons, may be closed by secondary suture when bacterial checks in the laboratory prove that closure of the wounds is permissible.

My answer to these three proposals in general is that they represent the point of view that prevailed during the War of 1914-1918. That our results then were most unsatisfactory no one now attempts to deny.

With regard to the use of plaster, thousands of surgeons are now prepared to assert that properly applied plaster-of-paris casts may and

* At this point slides were shown to demonstrate the technique of skeletal traction, fixed traction in casts and tables showing clinical results.

should be used immediately after compound fractures. If such fractures are reduced, if the limb is put in the cast in correct length and position and if the wound is protected against secondary infection, this represents, to many of us, ideal treatment (which permits transportation) under any circumstances.

With regard to temporary splints and secondary debridement, this involves secondary trauma to the wound, disturbance of the limb and the patient, and revision of the fracture. Many of us feel that such treatment is quite wrong. Primary reduction, direct or indirect fixation in plaster-of-paris casts and with no change for several weeks is much to be preferred. This method is in extensive use here and in war areas abroad.

With regard to the closure of wounds, there are practically no such wounds such as those described by the Committee as suitable for primary or secondary closure. We are not much concerned about abrasions and skin wounds, but for those which do involve tendons, joints and bones, more important surgery, operative and postoperative, primary and secondary is required.

The outline of treatment proposed in the Committee's report is an outline which was carefully considered, thoroughly tried and largely discarded after our military experience twenty years ago.

One of the common misconceptions with regard to the infrequent-dressing method is that the patient is likely to become septicemic, pyemic or toxic as a result of foul smelling dressings or casts. That a bad odor is a necessary concomitant of this method is an entirely erroneous idea. Such wounds and discharges as do have bad odors, have them because of contamination with certain saprophytes that occurs at the time of injury, at the time of operation, or quite often because of careless secondary dressings. In most of our cases, whether of wounds or compound fractures, no postoperative odor is associated with the case at all. The patients we receive late, after they have been contaminated already, are sometimes difficult to clean up and for a time may have disagreeable odors. Even such cases, however, can usually be kept clean and dry so that the odor disappears. Then they make a satisfactory convalescence without further difficulty from odor or otherwise.

Another misunderstanding as to skeletal fixation is that the primary reduction and fixation of the limb must undergo revision and readjustment if it is found that the fracture surfaces are not perfectly approxi-

mated. Spaces between the ends of the fractured bones will fill in with callus and bone repair if they are truly immobilized in correct position and are undisturbed during convalescence. No delay in union is to be anticipated even if the fragments are slightly separated.*

A diversion that is a common cause of inefficiency in fracture treatment arises out of the idea that the patient will be better off if he is made ambulatory. There is seldom any justification for trying to get a leg or femur fracture patient on his feet. As for moving joints in the vicinity of fractures, this is still as wrong as it was before skeletal fixation was invented. Certain complications, such as localized infection, failure of union and even stiffness of joints are much more likely to occur in any ambulatory fracture patient.

A final point that I should like to emphasize is that it is seldom necessary to experiment upon the patient with new methods or techniques. It is quite possible to decide upon theoretical grounds whether a new treatment is likely to do more harm than good. If a proposed treatment is inefficient for fracture reduction, if it fails to provide or prevents adequate drainage of an infected wound, if there will be motion or muscle spasm or pain in a fracture area, if the fracture must be readjusted after reduction, or if the wound must be traumatized or exposed to reinfection, the new method is probably not worth a trial. It will usually be better to adhere to the methods we now have and that do not neglect or violate the fundamentals of reduction, asepsis, drainage, immobilization and rest.

It is always the duty of the surgeon, not only to provide proper conditions for recovery, but to protect the patient, as far as possible, against his own voluntary, or involuntary, violations of the treatment regime, or other indiscretions.

* The contention that the ends of the fragments separate because of absorption and must be brought together by secondary adjustment is also wrong. If the fragments are in correct position and truly immobilized from the beginning, absorption at the ends will not occur.

EVALUATION OF DRUGS USED IN THE TREATMENT OF CARDIOVASCULAR DISEASES *

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To make an evaluation of all drugs used in the treatment of heart diseases in the time allotted to me is obviously impossible. Since I cannot cover the whole field, I will limit myself to those problems in drug therapy that seem to me to be of greatest interest. Drugs are, of course, not the only forms of treatment used in cardiology. Bed rest, diet, nursing care, physical therapy and, not the least, psychotherapy, all play important roles in the management of any patient with heart disease. Thus, in discussing certain phases of drug therapy tonight, I do not want to leave the impression that other therapeutic measures are either unimportant or unnecessary.

In presenting treatment from the standpoint of the drug rather than that of the patient we are not following the usual pattern. The point of view is that of a pharmacologist rather than that of the clinician. Although as a general rule this method of presentation is the least desirable, still there are certain advantages in so doing occasionally. A doctor is inclined to get lazy in his thinking after the diagnosis is made, and he may then prescribe potent remedies without having any more knowledge of the underlying actions and potential dangers of these drugs than the patient has to whom he is giving them. The doctor thus needs these facts brought to his attention, and an occasional review of basic pharmacology is desirable. I would suggest that a good textbook of pharmacology of recent vintage be available for ready reference on every doctor's bookshelf.

Digitalis is still one of the most important drugs used in the treatment of diseases of the heart. Its chief use is in the treatment of congestive heart failure, although it can sometimes be used to control the rapid ventricular rate of auricular fibrillation when heart failure is not

* Read before the Graduate Fortnight at The New York Academy of Medicine on October 16, 1941.

present, and to reduce the number of ventricular premature contractions when they are bothersome. It would seem hardly necessary to take up much time on digitalis except for the fact that some interesting developments have occurred in the last few years. We need not discuss the importance of controlling the use of digitalis by a preliminary period of bed rest until weight is constant, and after digitalis is given by noting the weight loss, by charting the ventricular rate in the case of auricular fibrillation and by noting daily the changes in the patient's symptoms and physical signs; nor is it necessary to point out that the initial digitalization must be made rapidly so that the concentration of digitalis in the body will be built up rapidly. I will leave the familiar aspects of digitalis therapy, therefore, to discuss two important developments in the digitalis field. These have occurred in the matter of bio-assay and in the use of the pure glycosides to replace the powdered leaf and the tincture.

The U. S. Pharmacopoeia in the Twelfth Revision has finally adopted the cat method of assay as official and the monograph is now in the process of being written. For many years clinicians have known that preparations of digitalis standardized on the cat are much more reliable than those standardized on the frog. Quite recently Gold et al¹ have shown by direct studies on man that the assay on the cat more closely approximates the values that we want than the assay on the frog. After all, the only purpose of a biological assay is to give us some indication of the possible potency in man. If the assay does not do this, as it apparently did not do with the frog, the assay is valueless. The term "cat unit" should be discouraged because the unit which will be established is not an absolute unit based on a lethal dose for a cat, but is a comparative unit based on the results obtained by cat assay on an unknown in comparison with a simultaneous cat assay on the standard pharmacopoeial digitalis powder. "Digitalis unit" will be the only term used regardless of the method of bio-assay. All preparations of digitalis should be checked on man because even the cat assay, although closer than the frog, may occasionally be off, particularly if the digitalis contains an unusually large amount of a slowly eliminated fraction. The suggestion has been made that all assays should be made in man and that the changes produced in the electrocardiogram should be used as the endpoint. However, anyone who has had a reasonable amount of experience with the effects of digitalis on the electrocardiogram will

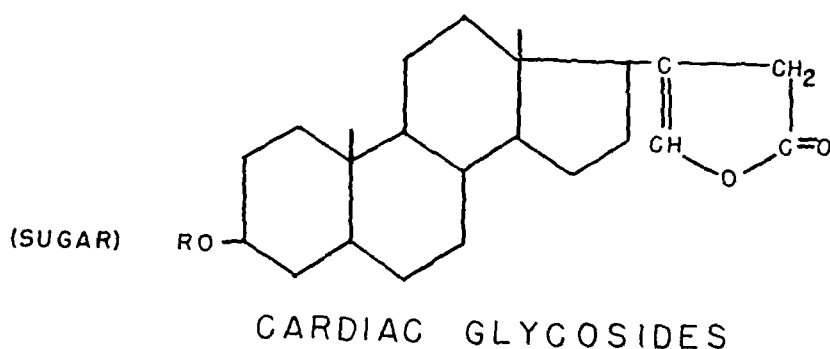


Fig. 1. Chemical Structure of the Cardiac Glycosides

know that there is no constant relationship between the therapeutic and toxic doses of digitalis and the electrocardiographic changes. Recently a carefully controlled study by Geiger, Blaney and Druckemiller² caused them to come to the conclusion "that the electrocardiogram has no practical clinical value for the quantitative estimation of digitalis saturation of patients." They found that the depression of the ST segment and diminished amplitude of the T waves occurred in less than one-half of the electrocardiograms of digitalized patients and that the onset and progression of such changes, when they did occur, were unrelated to the amount of digitalis that had been given. It is only in very carefully selected patients that the ventricular rate in auricular fibrillation can be used for comparative digitalis studies, and then the conclusions must be drawn only with extreme caution. The ventricular rate in some patients with auricular fibrillation may fall to normal on bed rest alone. Other patients who have had a rapid ventricular rate before digitalis, on digitalization develop a slow rate and then, in spite of the fact that no digitalis is given for several weeks, the ventricular rate does not return to the original level.

Since the cat assay, even though it is better than the frog assay, occasionally gives false information as to the anticipated potency in man, search is still being made for a better method of bio-assay. Let us hope when such a method is found it will not take a twenty years' fight to make it official. A method which looks promising is the embryonic chick heart assay method, first described by Paff^{3,4} and now being investigated in our laboratory. It has the advantage of lower cost, shorter time for the assay, and greater availability of biological material.

In the meantime, investigation on the pure glycosides found in digitalis and other related pharmacological substances has progressed to the point where it would appear that eventually these pure substances will entirely replace the crude drug and the need for bio-assay will no longer exist.

The chemical structure of the cardiac glycosides is interesting in that it contains the sterol nucleus which is common to the estrogens and androgens, corticosterone, vitamin D and cholesterol (Figure 1). The occurrence of this nucleus, particularly in common with the hormones found in the body, naturally arouses interesting chemical speculations. The butyro-lactone ring is contained in the basic structure of the genin or aglucone. Variations in the genin occur with various substituent groups on the nucleus. The desoxy sugar is attached at number 3 position. The term "glycoside" rather than "glucoside" should be used because a desoxy sugar is always present and glucose is frequently absent and, furthermore, if present, is not essential for the glycoside action.

Many modifications are possible both in the genin and in the attached sugars. Thus, when we speak of cardiac glycosides we speak of chemically related and not identical substances. Like the series of amines related to ephedrine, where variations in action are noted, for example between ephedrine and neo-synephrin, we must expect variations in the actions of the individual cardiac glycosides. There are differences in rates of absorption, differences in rates of elimination, as well as other pharmacological differences. The cat assay is particularly unreliable when applied to the cardiac glycosides. For instance, a patient can be maintained on about one-quarter the cat assayed amount of Digitoxin as he can on powdered leaf. It is important, therefore, to learn the dose of each glycoside in terms of mgm. actual weight and not in bio-assay units.⁵

Mercurial diuretics are firmly established as essential drugs in the treatment of congestive heart failure not responding to digitalis. Dyspnea alone in the absence of edema has been shown to be relieved by the use of mercurial diuretics as shown by the vital capacity studies of Alsever and Levine.⁶ Fluid accumulations due to cirrhosis of the liver, thrombophlebitis, or abdominal neoplasms may be diminished by this form of therapy.

The necessity for the combination of theophylline with the mercurial salt is now thoroughly recognized. Manufacturers have followed

TABLE I

COMPARATIVE EFFECTIVENESS OF MERCURIAL DIURETICS WHEN ADMINISTERED BY THE ORAL, PARENTERAL AND RECTAL ROUTES

| Diuretic | Number of trials | Trials successful | | Number of patients | Patients successfully treated | |
|--|------------------|-------------------|----------|--------------------|-------------------------------|----------|
| | | Num-ber | Per-cent | | Num-ber | Per-cent |
| Salyrgan-Theophylline by mouth (5 tablets) | 56 | 40 | 71.5 | 29 | 22 | 75.8 |
| Salyrgan-Theophylline intravenously | 37 | 35 | 94.6 | 24 | 23 | 95.8 |
| Mercupurin intravenously | 60 | 55 | 91.7 | 30 | 29 | 96.6 |
| Mercurin suppository | 22 | 14 | 63.6 | 13 | 6 | 46.1 |
| Salyrgan (modified) suppository.... | 20 | 10 | 50.0 | 11 | 8 | 72.7 |

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the lead of mercupurin, the first mercurial diuretic to contain theophylline chemically combined with the mercurial salt. When originally introduced, the theoretical reason for the combination was that there was produced a more potent diuretic by the synergistic action of a mercurial with a xanthine. The effect was obtained, but not for the reason assigned by the original investigators, Issekutz and Vegh.⁷ The presence of theophylline in molar equivalents to that of the mercurial salt has been shown to prevent necrosis at the site of injection.⁸ Furthermore, the increase in diuresis over that of the simple mercurial was due to more rapid and complete absorption.⁹ Sloughs and ulcers, gangrene and other serious local complications formerly found as a common occurrence with the injection of mercurial diuretics are now exceedingly rare.

Although methods of administration other than by the intravenous or intramuscular route are now used, none are quite as effective (see Table I). The intravenous route is almost 100 per cent effective. At the time this table was made we had just completed our study on salyrgan-theophylline tablets administered by mouth to hospital patients with large amounts of edema.¹⁰ The results looked very promising. Subsequent studies on ambulatory patients, however, were not so encouraging. It would appear that the less retained fluid there is, the higher is the incidence of undesirable side actions, particularly gastrointestinal irri-

tation. It is our present opinion, therefore, that only in an occasional ambulatory patient is it desirable to use the tablets orally. The suppositories seem to be tolerated much better.

The possible toxic effects on the kidney are well known and should be watched for. The presence of increasing albumin, casts or a greater number of red blood cells are danger signals. Very rarely a patient may suddenly go into shock or even die shortly after an intravenous injection of a mercurial diuretic. This accident is fortunately very rare. Animal experiments have shown that sudden death shortly after the administration of a mercurial diuretic intravenously is probably due to ventricular fibrillation. Some mercurial diuretics produce this more readily, and with smaller doses than others. All mercurials, however, can give this effect if a large enough dose is used and injection is sufficiently fast. Two notes of caution are, therefore, to be considered in intravenous injections:

1. Never use more than 2 cc.
2. Draw up blood into the syringe before injection and then take plenty of time to inject.

Mercurial diuretics work more effectively if ammonium chloride, ammonium nitrate, urea, potassium chloride or other salts which in themselves have diuretic properties are given at the same time. Ammonium chloride in enteric coated capsules is probably the most convenient form and the one best tolerated by the patient.

One cannot well leave out of this discussion drugs used in the treatment of the anginal syndrome, since this condition is so common. Departing for the moment from our set plan to discuss drugs only, we might briefly review the important points in treatment.

First and foremost is the necessity for a correct diagnosis. Every pain in the chest is not the anginal syndrome. Second, the anxiety factor is prominent and psychotherapy is, therefore, necessary. Third, supportive treatment is often more important than so-called specific therapy. This includes the use of sedatives. Also might be mentioned the relief of flatulence by some member of the atropine group, of which novatropine is probably the best example. Fourth is specific therapy directed towards dilating coronary arteries. The main drugs in this group are the nitrites and the xanthines.

Of the nitrites, nitroglycerine is still pre-eminently the best. The nitrites relax all smooth muscle, for instance in the bronchi, in the biliary

tract and in the intestine, if spasm is present. Relief of pain, therefore, when nitroglycerine is used does not presuppose the presence of coronary artery disease. The longer acting nitrates, such as erythrol tetranitrate and mannitol hexanitrate, have a limited use because many patients develop side actions.

The greatest controversy at present exists over use of the xanthines, particularly aminophylline. It might be well to review briefly the evidence for and against their use.

In a perfused rabbit's heart Fowler, Hurewitz and Smith¹¹ found that aminophylline caused greater and more consistent increase in coronary flow than any other member of the xanthine group. These observers also found that the drug when given by mouth to dogs after ligation of a coronary artery promoted an extensive collateral circulation. Wiggers and Green,¹² also working on dogs concluded from their experiments that "an increase in collateral circulation sufficient to be of functional use cannot be attained by use of vaso-dilating drugs after complete coronary occlusion." Gold, Travell and Modell¹³ ligated various coronary arteries in cats and then found that intensive use of aminophylline for three weeks produced no effect on the systemic blood pressure, or the course of the electrocardiographic changes nor did it reduce the size of the infarct. The weight of experimental evidence would indicate that little if any increase in coronary bloodflow would result from the use of aminophylline. However, in man, Levy, Bruenn and Williams,¹⁴ using induced anoxemia in patients subject to attacks of cardiac pain caused by coronary sclerosis, found that aminophylline injected intravenously caused a prolongation of 63 per cent in the time of appearance of pain. At the same time RS-T deviation was diminished by 58 per cent. When aminophylline was taken by mouth, there was a prolongation of 26 per cent in the time of the appearance of pain and the RS-T deviation was diminished by 32 per cent. This work would suggest some coronary artery vasodilation by aminophylline, more pronounced when given intravenously, but still noted in one-quarter of the patients when the drug is given by mouth. Riseman and Brown¹⁵ studied the effect of xanthines and other drugs on patients with the anginal syndrome using the exercise test as an objective method for measurement. They found that one-half of the patients were benefited by aminophylline if a large enough dose were used. However, clinical tests controlled by placebos have shown that aminophylline or other xanthines have no superiority

over the placebos.^{16, 17, 18}

It is evident then that there is considerable doubt as to whether or not aminophylline is of value as a coronary vasodilator in man. However, no investigator has found the drug to be dangerous, when given by mouth, so it can, therefore, be safely assumed that even though the aminophylline may do the patient no good, it can certainly do him no harm.

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TREATMENT OF LEUKEMIA BY
RADIOACTIVE PHOSPHORUS*

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LEUKEMIA presumably arises more or less focally, as in marrow or lymph nodes, and only subsequently progresses to involve other tissues than those normally concerned in the production of leukocytes. Nevertheless, as observed clinically in the human subject, it is invariably a generalized disease. Thus, it is not at present conceivable that any method of regional treatment can do more than palliate by causing regression of the main symptom-producing foci.

Yet the method of treatment chiefly relied on in the past three decades for the palliative treatment of leukemia has been local irradiation, especially by x-rays. This has been a natural consequence of the discovery that leukemia is a radiosensitive process, and of the gradual development of roentgen therapy as applied to various neoplastic processes.

While striking remissions can be caused by suitable local irradiation, directed to spleen, lymph nodes, bones, or other sites of leukemic infiltration, admittedly this focal attack is at best only an expedient, and leaves much of the disease untreated, so that eventually the process as a whole progresses beyond control and the patient dies. Statistical studies of results of local irradiation for leukemia show that there may be at best a lengthening of duration of survival by only a few months, although undoubtedly during the patient's remaining span of life he may secure notable remissions which otherwise he could not hope to have. While the occasional patient may survive for ten years or more, most of them die within three years. About 6 per cent of patients with chronic myelogenous leukemia and about 9 or 10 per cent with chronic lymphogenous leukemia survive five years from the beginning of treatment.¹

Recognizing the fallacy of attempting to control leukemia, a generalized disease, by local irradiation, numerous workers, particularly in

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the past decade have sought to treat the disease in toto by so-called spray irradiation of large segments of the body or by total body irradiation. These methods bring about a nearly uniform distribution of radiant energy throughout large segments of the body or the whole body. To be effective in palliation, the dose must be kept within the limits of the patient's tolerance, and at the same time must be sufficiently great to have an appreciable effect on the radiosensitive leukemic tissues. The principle on which this irradiation of all the body tissues is based is the differential in radiosensitivity between leukemic and normal tissues. While notable palliations are observed in many instances in the treatment of leukemia by spray or whole body irradiation, the obvious limitation lies in the fact that the patient's tolerance of whole body irradiation is nowhere near sufficiently great to permit taking full advantage of the differential in sensitivity between leukemic and normal tissues.

If, then, it became possible to deliver radiant energy in considerably higher concentration to the leukemic tissues which are usually more radiosensitive than the normal cells, the damage done to the leukemic tissues would be greater than to the normal tissues, and therefore we would approach a more nearly ideal method of treatment of leukemia by irradiation.

This ideal seems to be approached by radioactive phosphorus therapy. Yet it is necessary to keep in mind that treatment of leukemia by radioactive phosphorus is simply another method of whole body irradiation, and that probably it will be found sooner or later that no form of irradiation is the answer to the problem of the treatment of leukemia.

PHOSPHORUS METABOLISM IN LEUKEMIA

The importance of phosphorus as an element in the metabolism in leukemia is emphasized by Forkner² as follows:

"In chronic leukemia, untreated or not recently treated, there is usually a marked elevation of the blood phosphorus due to the total phosphorus content of cells, especially immature white cells. The phosphorus of the plasma varies greatly but remains within normal limits.

"Treatment of leukemia with roentgen rays or by means of radium results in a further increase of organic phosphorus in the blood and a transitory marked increase of organic phosphorus in the plasma, these values returning to normal as the patient is benefited and as the leuko-

cytes approach normal values in the blood.

"No variations of inorganic phosphorus occur in the plasma or cells before, during or following treatment with roentgen rays."

Studies made within the past year by Abels³ at Memorial Hospital of the post-irradiation changes in the organic phosphorus in the blood of patients with leukemia showed a marked agitation of organic acid soluble phosphorus levels in the leukocytes and usually in the erythrocytes after administration of radiation by any one of three methods: radioactive phosphorus, precordial x-ray therapy, and whole body x-ray therapy. The administration of non-radioactive phosphorus was not followed by significant alterations in phosphorus content of the blood cells.

Lawrence and his co-workers^{4,5,6} of the University of California have shown both in mice and in humans that radiophosphorus given in the form of sodium phosphate concentrates at first in the bone marrow and those tissues infiltrated with leukemic cells, and later concentrates in the osseous tissues.

Tracer studies made at Memorial Hospital by John Kenney⁷ have confirmed the fact that leukemic tissues pick up radioactive phosphorus in greater concentration than do normal tissues. What we term the differential absorption ratio for various tissues is determined as follows:

The amount of P-32 actually present in a given weight of a particular tissue as determined by measurement by means of the Geiger counter is divided by the amount of P-32 that would be present in the same weight of tissue were the administered amount, corrected for decay, evenly distributed throughout the body. In this manner it has been found that while normal lymph nodes show a differential absorption ratio of from 1.2 to 2.2, lymphosarcomatous or leukemic nodes show a differential ratio of from 2.2 to 12, averaging about three.

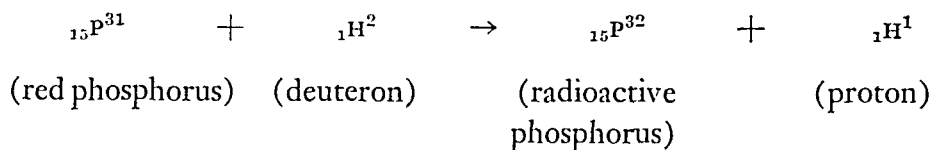
The factor of loss of active substance is also of great importance, loss by failure of absorption, by excretion, and by decay of radioactivity. Loss in the stools during the first four days after administration of an oral dose of P-32 depends on the amount given, and may total from less than 20 per cent to as much as 50 per cent. After the first four days the daily loss in the stools is less than 1 per cent of the retained body dose. Urinary excretion during the first 4 days totals about 10 per cent of the administered dose, and thereafter averages less than 1 per cent of the retained body dose per day.

The rate of disintegration of the radioactive material is also impor-

tant. Since the half-life of P-32 is 14.3 days, it follows that in three weeks 75 per cent of the administered material has decayed.

Taking into account these sources of loss, it is obvious that in three weeks very little activity remains. Thus there is little fear of unduly prolonged radiation effects from P-32.

Radioactive phosphorus or P-32, like other artificially produced radioactive isotopes, is a product of the cyclotron or so-called atom smashing machine. Ordinary red phosphorus with an atomic weight of 31 is bombarded by nuclei of heavy hydrogen (deuterons) moving at a high velocity (energy 16 million electron volts). The result is that about one in every million atoms of the red phosphorus is converted to radioactive phosphorus with an atomic weight of 32 (hence the term P-32). The following equation presents the reaction:



P-32 disintegrates at an exponential rate. Its "half-life" is 14.3 days, that is after every 14.3 days there remains only 50 per cent of what was present at the beginning of that period. The end product of the disintegration of P-32 is sulphur, ${}_{16}\text{S}^{32}$.

P-32 is measured in millicuries, as is radon (radium emanation), based on the number of atomic disintegrations per unit of time. When a sample emits 3.7×10^7 beta particles per second it is said to contain one millicurie. It is a peculiar and probably fortunate property of P-32 that its disintegration causes the emission, not of alpha and beta particles and gamma rays as does radon, but only of beta particles, which have a penetrating power in tissue of only about 2 mm. on the average.

It is estimated, for purposes of comparison with x-ray therapy, that 1 millicurie retained for twenty-four hours by an adult of 70 kg. weight, would deliver the equivalent of 0.6 roentgens of whole body radiation.

Through the courtesy of John H. Lawrence of the University of California we have received at Memorial Hospital for the past 2 years regular shipments of an aqueous solution of dibasic sodium phosphate containing about 15 milligrams of phosphate per cc. of solution, representing a mixture of radioactive and inactive phosphorus. (About one in every million atoms of the phosphorus is radioactive.)

Upon receipt each shipment is re-measured for its radioactivity per cc. It is then a simple matter to measure out from day to day individual doses as requisitioned, making of course, proper correction for the rate of loss by disintegration.

P-32 may be given orally, intravenously, or by other parenteral routes.^{8,9} We have used the oral route almost routinely. In some instances we attempted intravenous use of the solution sterilized by boiling after its receipt in New York, but found such an incidence of reactions evidently due to some pyrogenic substance that we felt it unsafe to continue intravenous administration, unless the material were to be made sterile at the source. The only disadvantage of the oral route is that about 25 per cent is lost through the feces.

DOSAGE OF P-32 IN LEUKEMIA

In the beginning of our work with the treatment of leukemia by P-32 we used fairly large single doses at intervals of about a week. However, certain evidence has accumulated that has led us to believe it preferable, after evaluation of the patient's status, to select a certain dose related definitely to the patient's body weight and to divide this dose into 5 to 7 fractions, to be administered one a day. This division of dosage apparently reduces the excretory loss of phosphorus and probably favors a more complete pick-up by the leukemic cells.

The evaluation of the patient's status is fully as important if not even more so, as in selection of dosages of conventional radiation. The general condition of the patient, the degree of acuteness or chronicity of the leukemic process, as reflected by both clinical and hematological findings, and in particular the degree of remaining erythropoietic activity in the marrow, as estimated by sternal puncture, are the main factors considered in deciding what dose of P-32 to give.

To an adult in good general condition with chronic leukemia, and with evidence by sternal puncture of good erythropoiesis, the first total dose may amount to 70 to 100 microcuries per kg. of body weight. Thus to such an adult weighing 70 kg. a total of 5 to 7 millicuries may be administered in fractions of about 1 millicurie given daily for five to seven days.

To an adult in less favorable condition, with evidence of a more acute process, or with reduced erythropoiesis, the total dose to be administered in the first course may be reduced to as little as 20 microcuries per kg.

When trials are made of the use of P-32 in acute leukemia in children, we favor great caution in dosage, just as with conventional x-ray therapy.

In any less favorable case it seems advisable to begin with a single test dose, and observe the patient for two or three days to see what reaction if any is induced.

Depending on the response to the first course, subsequent courses may be given, usually in somewhat smaller dosage, leaving an interval of 1 to 2 weeks between courses. It is impossible to give any definite figure as to optimum total dosage.

Erf, Tuttle, and Lawrence⁴ state that their first doses were determined by the following considerations:

"The lethal dose of radio-phosphorus for a 20 gram mouse is approximately that amount given intraperitoneally which emits 70 microcuries of beta-radiation; for a 6 pound monkey, 7 millicuries by the same route. These results suggest that the lethal dose of radio-phosphorus for an average adult human would be well over one hundred millicuries."

Their figures for single lethal doses in animals may be computed to work out to 3500 microcuries per kg. for mice and 2600 microcuries per kg. for monkeys. For a 70 kg. adult their estimate of 100 millicuries would be a conservative one of only about 1400 microcuries per kg. However, I believe it should be noted that any estimate of a lethal dose of radiation for a normal animal or human may need to be considerably modified when applied to a leukemic patient.

It would seem safer, for the present, to regard P-32 as a palliative, as another form of whole body irradiation. Many situations arise in cases treated by P-32 suggesting the addition of conventional local x-ray therapy. For example, when a patient who has had some treatment by P-32 shows a decrease of erythropoiesis in his marrow, but still has a large spleen or masses of nodes that have not satisfactorily regressed, suitable doses of local x-rays may be given such fields to advantage, with less risk of further depletion of the marrow than would be entailed by further P-32 therapy. It is noteworthy that the ingestion of radioactive phosphorus is not followed by symptoms of acute radiation sickness.

RESULTS

From February 1940 to date*, thirty-eight cases of leukemia have

* November 18, 1941.

been treated by radioactive phosphorus. The follow-up is complete. These cases comprise twenty-two of the chronic type, fifteen acute, and one eosinophilic. The results may be summarized as follows:

1. Eleven cases of chronic myelogenous leukemia of adults.

Three died in 20.5, 4, and 4 months respectively following the beginning of P-32 therapy. All three appeared to have had a good result and to be under control until shortly before death. Eight are living, 11, 11, 9, 5, 5, 3, 1 and 1 month since treatment began. Of the whole group of eleven cases, seven, including the one who died after 20.5 months, showed definite evidence that P-32 is an effective therapeutic agent in this type of leukemia. In two there was no control, and two others have begun treatment so recently that nothing can be said about results in them. The total doses used in those who have been treated over any extensive period have been from 260 to 960 microcuries per kilogram.

2. Acute and subacute myelogenous leukemia, one case of each. Both patients died, one in one week and the other in six weeks, with no detectable effect of P-32, favorable or unfavorable.

3. Chronic lymphatic leukemia of adults, eleven cases.

On the whole this group has been less favorable than the chronic myelogenous cases, in that most of them were well along in their course and had had a considerable amount of previous x-ray therapy. Five died from two to ten weeks after P-32 was begun. One of these had so little treatment and for such a short time that his case could fairly be disregarded. Six are living, 12, 11.7, 10.3, 5.8 and 4.6 months.

Three or possibly four of the whole group of eleven have had real evidence of control of the disease by P-32; three living, 12, 11.7, and 10.3 months and one who showed some evidence of control but who died in two months, with splenic infarction.

The favorable effects seen in chronic lymphatic leukemia have been mainly the regression of enlarged spleens and lymph nodes, while in general the blood and marrow have not been notably influenced.

The doses for those for whom it was possible to give treatment for any considerable period were from 150 to 350 microcuries per kg.

4. Acute lymphatic leukemia of adults. Two cases, both in young women with no benefit from P-32, death occurring within a few weeks.

5. Acute lymphatic leukemia of childhood, eleven cases. Nine patients died in from one week to five and one-half months after P-32 was first administered. No real effect was seen in any of these, although

one, a five-year-old boy, who received 200 microcuries per kilogram, went home in poor condition, yet did improve for a time, and survived longer than we had expected, however, only $3\frac{1}{2}$ months in all.

Two children are still living, one for three months, and still under treatment and having shown a slight effect on nodes; the other over four months and with a remarkable remission. In this case there was some discussion as to whether the result was that of sulfadiazene on an atypical acute infection with positive blood culture of hemolytic *Staphylococcus aureus* and a leukemoid picture, or a true remission of leukemia perhaps aided by P-32. A recent relapse, however, gives clear indication of the leukemic nature of his illness.

6. One case of eosinophilic leukemia in a girl of nine years, who also has rheumatic heart disease. She has survived six and one-half months since P-32 was first administered. She was treated from April 28 to July 19, 1941, receiving 260 microcuries per kilogram. On admission her white cell count was 134,600, with 90 per cent eosinophiles. Her spleen extended three fingers' breadth below the costal border and she had a slight general adenopathy. The red cell count was 3.7 million and the hemoglobin 56 per cent.

On October 16, her hemoglobin was 90 per cent, red cell count 4.2 million, white cell count 7,250, with 8 per cent eosinophiles. The nodes had disappeared, and the spleen was only one finger's breadth down. The liver remained very large, but she is a cardiac cripple and we believe the large liver mainly due to the cardiac condition.

SUMMARY AND CONCLUSIONS

1. Radioactive phosphorus offers a means of irradiation whereby leukemic tissue throughout the body may be somewhat selectively treated, without fear of undue retention of radioactive material. For purposes of rough comparison the method may be regarded as somewhat analogous to the Heublein or spray methods of whole body irradiation, with the possible advantages offered by the differential absorption ratio and the localized character of the P-32 irradiation.

2. P-32 is probably best regarded as simply another means of palliation for leukemia, and may be best used in many cases in conjunction with conventional local irradiation.

3. It is too early to attempt to compare the results of whole body irradiation by P-32 with those of spray irradiation by external sources

or Heublein therapy. However on theoretical grounds P-32 offers the advantage of more or less selective irradiation of leukemic tissues.

4. The results of treatment for leukemia have been as follows:

Chronic myelogenous leukemia. Excluding two cases whose treatment has been started in the past few weeks, seven of nine have shown clinical and hematological improvement.

Chronic lymphatic leukemia. In a rather unfavorable group of eleven cases, four at the most have shown a good response, by regression of spleen and nodes, without much effect on the blood or marrow.

Acute leukemias. Thirteen of fifteen have shown no evidence of favorable response. One survivor has been under treatment only three months and is still in a precarious state, while one has survived four months and has shown a remarkable remission, until very recently.

Eosinophilic leukemia. One case, with survival of six and one-half months, with remission attributable to P-32.

5. The study of the use of P-32 in institutions where control of dosage by accurate physical measurements is possible has not yet progressed to the point where it is safe to recommend the release of this potent agent for general therapeutic use.

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1. Grateful acknowledgement is accorded to John H. Lawrence for furnishing radioactive phosphorus from the Berkeley cyclotron of the University of California, and for his helpful advice; to C. P. Rhoads, Medical Director of Memorial Hospital, for his aid in furthering this project; to John Kenney, who most efficiently planned and carried out the details of this work; to Gioacchino Failla, Edith H. Quimby and Mr. L. D. Marinelli of the Department of Physics; to Helen Q. Woodward of the Department of Chemistry, and to Fred W. Stewart, Pathologist.
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THE ADRENAL CORTEX AND ELECTROLYTE BEHAVIOR

Harvey Lecture, December 18, 1941

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THE gradual growth of knowledge concerning the functions and interrelations of the endocrine glands has undergone gratifying acceleration in the last two decades. This progress has resulted primarily from the integration of clinical and physiological studies which have gained both in scope and importance through the dramatic advances of organic chemistry. Identification and synthesis of the chemical compounds normally elaborated in the glands of internal secretion have furnished the clinician and physiologist alike extraordinary opportunities for controlled observation. The study of the effects of these various compounds in spontaneous disease and their action in pathological states arising from ablation of endocrine structures as well as the observation of their effects in intact animals has proved most profitable.

In the past fifteen years interest in the adrenal glands has been focused upon cortical function. It has become apparent that control of a number of significant and apparently quite dissimilar physiological activities is invested in the outer layers of the suprarenal capsules. These activities, hormonal in origin, are now known to include carbohydrate metabolism, electrolyte and water metabolism, and probably others. It is my purpose this evening to review primarily the role of the adrenal cortex in relation to electrolyte behavior.

The syndrome of salt loss and dehydration with its resultant state of shock is characterized clinically by progressive weakness culminating in overwhelming prostration, increasing pulse rate associated with falling blood pressure, subnormal body temperature, nausea and vomiting, sunken eyes, and loss of normal turgor of the subcutaneous tissues.¹ Examination of the blood in these states of dehydration reveals an increase in hematocrit and serum protein, i.e., decrease in water content, a decrease in bicarbonate or chloride content of the serum or a decrease in

both accompanying a fall in sodium. When the development of this syndrome is rapid there is also an increase in urea, which appears before the final stages of oliguria or anuria develop. The correlation of these clinical and chemical disturbances was first established in patients with cholera by O'Shaughnessy² in 1831. O'Shaughnessy also demonstrated that the intravenous administration of salt and water had a most salutary therapeutic effect. The similarity of the state of dehydration and shock in cholera to that in diabetic acidosis gave rise to the treatment of the latter condition by the intravenous injection of saline solution by Hilton Fagge³ in 1874. Since that time the presence of the syndrome of dehydration and shock has been recognized in a number of conditions in which the physiological disturbance results primarily from the loss of inorganic base.

The interest of a group* at the Presbyterian Hospital in problems of adrenal physiology developed as a by-product of a long series of studies on electrolyte and water metabolism in normal individuals and in certain morbid states and was not initiated by a particular interest in the endocrine field. The obvious similarity of the syndrome of salt loss and dehydration to the familiar clinical picture of acute adrenal insufficiency in man, however, led us nine years ago⁴ to make chemical surveys of the blood of a number of patients with Addison's disease. The abnormalities encountered were indeed striking and included a decrease in the sodium concentration of the serum with a corresponding drop in chloride and bicarbonate, an increase in potassium content of the blood serum, a variable increase in non-protein nitrogen, inorganic phosphorus and sulfate and calcium as well as hemoconcentration, i.e., decrease in plasma volume. Since that time we have had the opportunity of making similar observations in more than sixty patients with Addison's disease and the results obtained are in agreement with our initial findings and with those of Harrop,^{5,6} Thorn,⁷ Wilder,⁸ and many others. Furthermore, they are analogous to those of Baumann and Kurland⁹ made in 1927 in adrenalectomized cats.

The decrease in serum sodium concentration in the first three patients studied was impressive and in the third case, after the sodium had dropped under observation to 108.7 m.eq. per liter (Table I), the patient was treated with salt solution¹⁰ following which she made a remarkable recovery, having literally been in extremis when therapy was instituted.

* Drs. D. W. Atchley, J. Stahl, J. W. Ferrebee, C. A. Ragan, Jr., D. Kuhlmann, D. Parker, and others.

TABLE I

CORRELATION OF BLOOD CHANGES WITH SALT FEEDING AND SALT WITHDRAWAL IN A PATIENT WITH ADDISON'S DISEASE

| <i>Date</i> | <i>Na</i> | <i>K</i> | <i>Cl</i> | <i>HCO₃</i> | <i>Non-Protein Nitrogen</i> | <i>Blood Pressure</i> | <i>Remarks</i> |
|--------------|---------------|---------------|---------------|------------------------|-----------------------------|-----------------------|--|
| | m. eq. per l. | m. eq. per l. | m. eq. per l. | m. eq. per l. | mg. per 100 cc. | | |
| July 19 1932 | 123.5 | 5.3 | 88.6 | 21.8 | 39.0 | 85/55 | Blood taken shortly after admission. Profound weakness and vomiting. |
| July 26 | 107.8 | 7.1 | 72.7 | 21.5 | 45.0 | 65/48 | Critically ill. Almost in extremis. No therapy up to this time. |
| Aug. 2 | 133.0 | 5.1 | 93.8 | 27.5 | 20.6 | 84/60 | Treated with a single dose of Eschatin and then NaCl daily. No more vomiting, sitting up. |
| Nov. 14 | 139.9 | 4.6 | 107.3 | 24.3 | 20.0 | 112/74 | Up and about at home, doing part of housework. Eats 7 gms. of NaCl daily plus diet. Slight puffiness of eyelids. |
| Jan. 24 1933 | 126.8 | 5.7 | 92.3 | 21.2 | 35.0 | 86/60 | After 7 days salt-poor diet, weak and vomiting frequently. Confined to bed. |
| Jan. 30 | 138.0 | 5.0 | 103.5 | 25.9 | 25.0 | 122/80 | After no further treatment except NaCl added to diet and given by rectum. No vomiting. Much stronger. |

Subsequently, salt was withdrawn from the patient's diet with the result that a moderate crisis was precipitated in 7 days. Following the readministration of salt and water, the patient improved strikingly and was able to return home. The clinical improvement was associated with the correction of the chemical disturbances observed in the blood serum.

These observations demonstrated, among other changes, that (1) the acute adrenal insufficiency of Addison's disease is usually associated with a sharp decrease in the sodium content of the blood serum, (2) that the withdrawal of the sodium ion from the diet may induce acute adrenal

SODIUM LOSS FOLLOWING ADRENALECTOMY IN DOGS

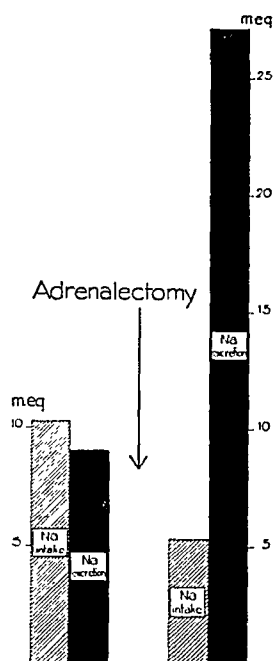


Fig. 1—Relation of sodium intake to renal sodium excretion before and after adrenalectomy. The great loss of sodium which follows adrenalectomy takes place through the kidneys.

insufficiency and that (3) this may be alleviated with correction of the various electrolyte disturbances by the readministration of salt and water. This is now an old and familiar story. Harrop, Soffer, Nicholson and Strauss¹¹ and also Allers¹² subsequently demonstrated that adrenalectomized dogs may be maintained in relatively good health for many months without the use of cortical extract, if given large enough amounts of sodium chloride to which is added sodium bicarbonate or citrate.

The next step in these studies was concerned with the mechanism by which the sodium concentration of the serum is reduced in adrenal insufficiency. For this purpose we studied in dogs the effects of adrenalectomy upon electrolyte balances as well as upon changes in serum electrolyte concentrations.¹³ Upon removal of both glands, the familiar chemical pattern of the blood in acute adrenal insufficiency appeared and this, among other changes, was associated with a striking increase in the excretion of the sodium ion (Fig. 1) as well as of chloride by the

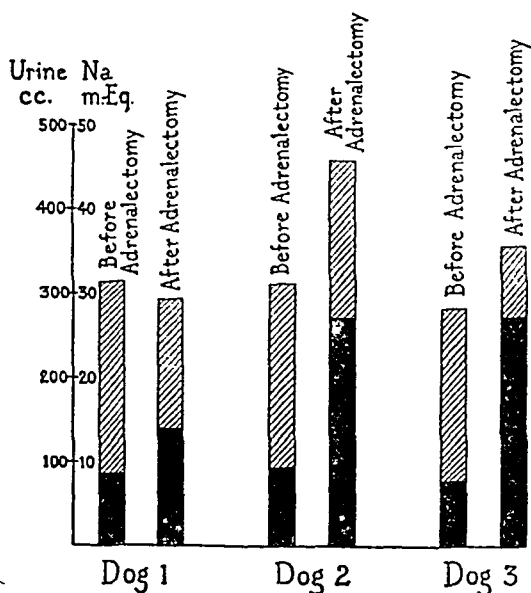


Fig. 2—The effect of adrenalectomy upon the excretion of sodium in relation to urine volume. The total columns represent the daily urine volume and the black columns the daily sodium excretion. The low values following adrenalectomy in Dog 1 result from including the terminal oliguria in calculating the average daily excretion.

kidneys. The loss of base was sufficiently great to indicate that sodium must have come from sources other than the blood stream alone. Not only was the renal excretion of sodium increased after adrenalectomy, but also the concentration of this ion in the urine was augmented despite the fact that the urine volume was greater in the first days after operation than before (Fig. 2). These observations, as well as the later studies of Harrop^{14, 15} demonstrated that the decrease in sodium content of the blood in acute adrenal insufficiency is dependent upon an increase in the renal excretion of this ion and not solely upon its internal redistribution. This is borne out by the recent studies of Muntwyler et al¹⁶ who found that, "The outstanding changes of the skeletal muscles of dogs in adrenal insufficiency were a loss of sodium and a gain of water." The lowered concentration of sodium in the blood serum and interstitial fluid following the increased renal excretion of this ion necessitates an osmotic readjustment which, according to Darrow and Yannet¹⁷ and Harrison and Darrow,¹⁸ is reflected by a gain in water limited to the cells. The idea that redistribution of water and sodium, as well as their

excretion, plays a significant part in adrenal insufficiency appears valid from the observations of Harrop,^{15, 19} Swingle and his associates,^{20, 21} and of Muntwyler et al.¹⁶ The evidence is based upon results obtained when large amounts of cortical extract are given to dogs in acute insufficiency during which both fluid and food are withheld for 24 to 48 hours. Under these circumstances, i.e., when there is no intake of sodium and its excretion is reduced by cortical hormone, there results an increase in the concentration of sodium in the blood serum. It is believed that this increase in serum sodium concentration is due to a shift of interstitial fluid to the blood stream, which results in hemodilution, followed by a more rapid excretion of water than of sodium. It is also believed that a shift of intracellular water contributes to hemodilution and increased water excretion, as well as to the augmentation of potassium excretion in this type of experiment.

After having ascertained that an unusually great loss of sodium takes place through the kidneys following the development of acute adrenal insufficiency, an attempt was made to pursue the mechanism of this disturbance a little further. Despite the fact that ketosis is, as a rule, insignificant in acute adrenal insufficiency and despite the fact that Harrop²² had found no increase in the lactic acid content of the blood in the adrenalectomized dog, nor we in a patient, it seemed necessary to establish whether or not the presence of some other organic acid might be responsible for the abnormal loss of fixed base. This problem was studied indirectly by determining the titratable acid and ammonia excretion in a patient²³ developing adrenal insufficiency under observation and also by following ammonia excretion in the adrenalectomized dog²⁴ deprived of cortical extract. In neither instance was an increase observed, as might have been anticipated were an organic acid to be excreted in large amounts. As a matter of fact, ammonia excretion actually decreased slightly with the advance of insufficiency. These observations were considerably extended by Jimenez-Diaz²⁵ who then explained the loss of sodium on the failure of the ammonia mechanism. This hypothesis does not appear to be tenable because the order of magnitude of the failure of the ammonia mechanism is not great and only becomes manifest relatively late in the development of cortical insufficiency.

In default of direct proof, it is tempting to assume that the increased excretion of sodium in adrenal insufficiency depends upon the loss of the normal power of reabsorption of this ion by the renal tubules. This

will be discussed in detail later.

Intimately related to the disturbances of sodium and water behavior in adrenal insufficiency are abnormalities in the behavior of the potassium ion. Baumann and Kurland,⁹ Hastings and Compere,²⁶ Zwemer,²⁷ Kendall²⁸ and others have commented upon the regularity with which, in animals, the concentration of potassium is increased in the blood serum. We observed a similar increase in patients with Addison's disease,²⁹ but the normal levels were exceeded with perhaps less regularity than in adrenalectomized animals.

From the physiological standpoint, abnormalities in the behavior of the potassium ion appear to bear a mirror image to those of the sodium ion. In contrast to the abnormally increased excretion of the sodium ion, Harrop¹⁴ showed that potassium is retained by adrenalectomized dogs. Subsequently Harrop³⁰ and Thorn³¹ showed that large amounts of cortical extract would increase the excretion of potassium and decrease the excretion of sodium in normal and adrenalectomized animals as well as in human subjects. The retention of potassium in acute adrenal insufficiency is not only demonstrated by its increase in blood serum but also by some increase in the muscle cells as shown by Darrow and his associates.¹⁸ This potassium retention in the cells is associated with an increase in intracellular water. As previously mentioned, the accumulation of water in the cells may, according to Darrow and Yannet,¹⁷ result from the osmotic disturbance initiated by the loss of sodium from the body. The mechanism for the abnormal behavior of potassium, like that of sodium, appears at least in part, to find its origin in the kidney. Thus, Harrison and Darrow³² have shown that the potassium ion is not concentrated normally by the kidneys of adrenalectomized animals even when they are maintained in good condition by the ingestion of extra sodium chloride. Furthermore, Talbott³³ has recently demonstrated that the potassium clearances of patients with Addison's disease are abnormally low even after prolonged and adequate treatment with desoxycorticosterone esters.

It has been pointed out by Zwemer²⁷ that adrenalectomized animals are killed by the ingestion or injection of relatively small doses of potassium salts. This observation can be explained on the basis of the lowered excretory capacity for the potassium ion and also by the fact that added potassium has been shown by Harrop,³⁰ as well as by Wilder and his coworkers,³⁴ to further the excretion of an already depleted supply of

sodium in the body. Despite the toxicity of potassium salts in the presence of adrenal insufficiency, it seems unlikely that potassium poisoning is the cause of death, at least in patients with Addison's disease. This is indicated by the fact that critically ill Addisonian patients with a marked decrease in serum sodium concentration at times show little or no retention of potassium in the blood serum.

It may be of interest to indicate here one point of difference between the state of dehydration resulting from the loss of base in diabetic acidosis³⁵ and in starvation ketosis on one hand and that of adrenal insufficiency on the other. In the former states both sodium and potassium excretion are increased, whereas in adrenal insufficiency sodium excretion only is augmented while that of potassium is diminished. This difference may be explained by the specific decrease in the renal clearance of potassium and possibly by decreased gluconeogenesis from body protein due to a loss of cortical adrenal function.

I should now like to comment on other changes in the activities of the kidney in adrenal insufficiency. In 1914, Gaillard³⁶ and also Porak and Chabanier³⁷ observed the presence of nitrogen retention and discussed alterations in renal secretion following ablation of the adrenal glands. Swingle suggested in 1933³⁸ that nitrogen retention develops because of a fall in blood pressure and a decrease in renal blood flow. This view is supported by observations of Margitay-Becht and Gömöri³⁹ who found marked decreases in creatinine clearance in adrenal insufficiency. Studies of Stahl, Kuhlmann and Urban⁴⁰ led to the same conclusion. Talbott³³ has recently made inulin and diodrast clearance studies on a group of Addisonian patients in whom the blood sodium concentration was maintained at a normal level. After treatment with desoxycorticosterone acetate had been continued for many months, these patients still showed disturbances in renal function as manifested by a decrease in the "filtration fraction" which suggested a diminution in efferent arteriolar tone. It seems likely that nitrogen retention and the retention of sulfate and phosphate in marked insufficiency may be in part accounted for by a decrease in renal blood flow or in efferent arteriolar tone. Whether or not the abnormalities of sodium and potassium metabolism and the decrease in ammonia excretion have the same basis is not known. It is possible that they have a more specific basis, i.e., one in which renal cellular function is altered through the lack of one or more substances normally elaborated by the adrenal cortex. For example,

Jimenez-Diaz²³ indicated in 1936 that the rate of deaminization of amino acids by kidney tissue of adrenalectomized animals is less than normal. This has recently been confirmed by Russell and Wilhelmi⁴¹ who suggest that, "the failure of the kidney to deal adequately with electrolytes after adrenalectomy may be related to an underlying failure in the energy-yielding processes of the kidney." This point of view may be extended to include nitrogen metabolism more generally, as Kendall⁴² has recently shown that concentrated cortical extract contains a substance other than desoxycorticosterone which lowers the blood urea without increasing sodium retention appreciably.

Regardless of the validity of these concepts, it is clear that a series of profound disturbances appears in the behavior of certain electrolytes and water when the products of adrenal cortical tissue no longer circulate in adequate amounts. It also is clear that these disturbances lead to dehydration, shock and death. It is also certain that the kidney plays an important part in this chain of events. Finally, it is certain that these disturbances can be dramatically corrected in patients with Addison's disease and in adrenalectomized animals by the simple procedure of administering large quantities of sodium salts and water. The same effects can be obtained with large amounts of cortical extract and an adequate supply of salt and water. If the intake of potassium is restricted, as shown by Wilder, Kendall et al,³⁴ still more gratifying results may be obtained from salt or cortical extract therapy. The similarity of these effects of salt and extract are shown in part in Fig. 3.

One observation has particularly impressed a number of workers interested in adrenal cortical function. When an animal in severe adrenal insufficiency is deprived of food and water, but is given a large dose of cortical extract, striking improvement may take place. This improvement begins before any demonstrable change occurs in the serum sodium, potassium or nonprotein nitrogen or the water content of the blood, i.e., before any obvious redistribution of fluid can occur.²⁴ This finding makes it apparent that the effect of cortical extract on an animal suffering from acute adrenal insufficiency is not limited to its effects upon electrolyte and water metabolism. In the light of present day knowledge, it seems possible that this immediate response to cortical extract may result from carbohydrate-active steroids in the extract. As long as only extracts of the adrenal cortex and not specific chemical substances elaborated by it were available for study, it was impossible to know definitely whether

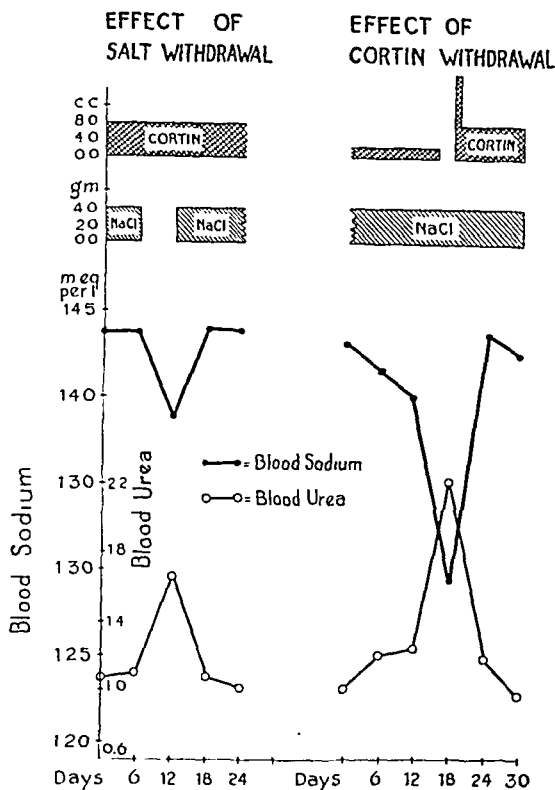


Fig. 3—Comparison of certain effects of the withdrawal of sodium ion from the diet with those of the withdrawal of cortical extract in an adrenalectomized dog, normally maintained with both. The effect upon the serum potassium level parallels that of the blood urea.

the effects on carbohydrate metabolism, the effects on electrolyte metabolism and other effects could all be mediated by one substance or whether different functions were dependent upon differences in chemical structure. In patients with Addison's disease we²⁰ were unable to demonstrate any correlation between the bouts of hypoglycemia and disturbances in the electrolyte pattern of the blood serum. That is, hypoglycemia occurred when the electrolyte pattern of the blood was entirely normal and conversely, in the presence of severe insufficiency with marked reduction in serum sodium, the blood sugar was usually within normal limits. From these observations it could be surmised but not established that different chemical entities might influence the carbohydrate and electrolyte functions more or less independently.

During the past four years the dissection of the specificity of adrenal cortical functions has been made possible principally by the chemical

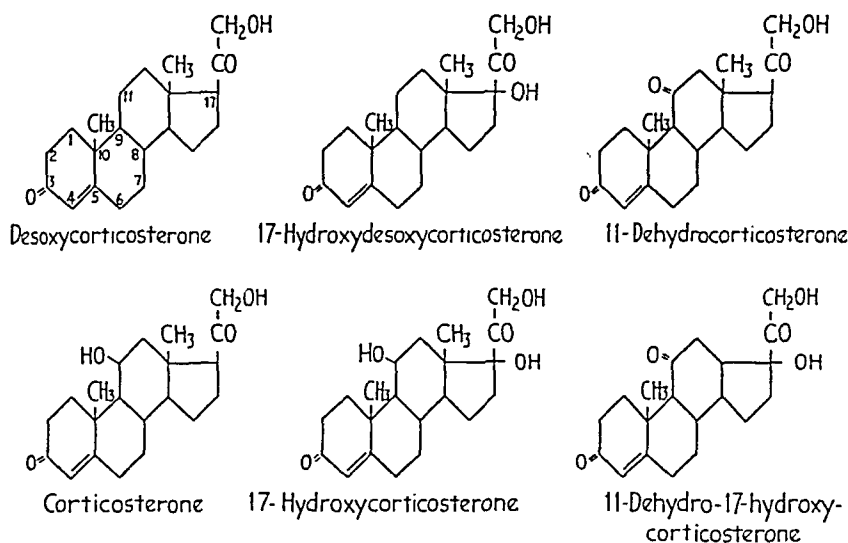


Fig. 4—Steroids with known physiological activity isolated from adrenal cortical tissue.

contributions of Kendall^{43, 44} and of Wintersteiner and Pfiffner⁴⁵ in this country and of Reichstein⁴⁶ in Switzerland. Up to the present time there have been isolated from the adrenal cortex according to Kendall,⁴² twenty-four different steroids. Of these six have been shown to possess physiological activity (Fig. 4). These include desoxycorticosterone, 17-hydroxydesoxycorticosterone, corticosterone, 11-dehydrocorticosterone, 17-hydroxycorticosterone and 11-dehydro-17 hydroxycorticosterone known as compound E of Kendall. How many of the steroids isolated from adrenal cortical tissue occur naturally and how many may appear as degradation products is not yet known. One of the cortical steroids namely desoxycorticosterone, was synthesized by Steiger and Reichstein⁴⁶ in 1937 and since that time its effect upon adrenal insufficiency has been extensively studied.

In England, Levy Simpson^{47, 48} first observed the clinical improvement of Addisonian patients following both the subcutaneous injection and implantation of pellets of desoxycorticosterone acetate. In this country, Thorn and his associates^{49, 50, 51} were the first to make similar but much more extensive studies both upon adrenalectomized dogs and upon patients with Addison's disease. Our own clinical studies^{52, 53} were en-

* All desoxycorticosterone and corticosterone used in our studies has been furnished through the courtesy of Roche-Organon, Inc., Nutley, N. J.

EFFECT OF TEN DAYS TREATMENT WITH DESOXYCORTICOSTERONE PROPIONATE

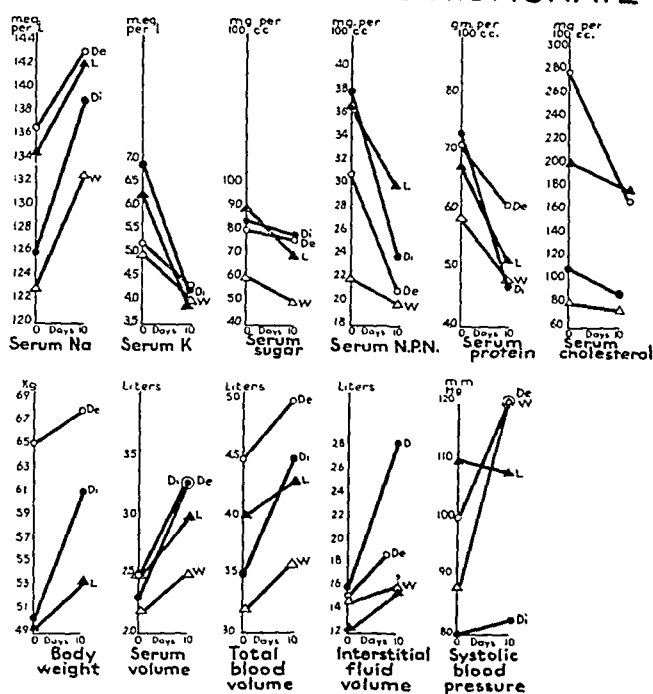


Fig. 5—Effects observed as a result of the administration of an average daily dose of 19 mg. of desoxycorticosterone propionate over a period of 10 days in patients with Addison's disease.

tirely confirmatory of Thorn's. It has become clear that the administration of desoxycorticosterone esters has the same qualitative effects upon water and electrolyte metabolism in adrenal insufficiency as does the administration of either large doses of sodium salts or large doses of the available commercial cortical extracts given in conjunction with salt and water. The magnitude of the effects of even small doses of desoxycorticosterone is much greater than can be obtained by the use of salt or of cortical extract.

The results of desoxycorticosterone treatment in patients with Addison's disease are now well known and can be briefly summarized (Fig. 5). The esters of this steroid cause striking retention of salt and water. The rate of retention of the sodium ion usually exceeds that of water so that, as a rule, the serum sodium concentration rises to normal and is maintained at a normal level as fluid retention continues. In some instances, however, water is retained more rapidly than sodium so that the sodium concentration of the blood serum may actually fall during

the first days of treatment. The amount of salt and water retained varies greatly in different patients and cannot be correlated with the initial serum sodium or protein concentration or with the initial plasma volume or with the severity of the disease. For example, one of our patients gained 11 kilos in the first 10 days of treatment with an average daily dose of 19 mg., and became markedly edematous. Another patient whose disease appeared to be equally severe gained but 2 kilos in 30 days with an average daily dose of 24 mg. The retention of salt and water is reflected by an increase in interstitial fluid volume as well as by increases from 300 to 1200 cc. in plasma volume in the first 10 days of treatment.

Potassium metabolism, like that of sodium, is profoundly influenced in adrenal insufficiency by desoxycorticosterone. Thus, the concentration in the blood serum is not only reduced to normal, but has been observed in some of our patients to fall as low as 2.4 m.eq. per liter. The urinary excretion of potassium increases regularly on the first day or two of hormone injection and thereafter becomes variable.

Disturbances of renal function, as measured by nitrogen retention and failure of ammonia excretion, are influenced within the first 24 hours of desoxycorticosterone administration. The recent studies of Talbott,³³ already mentioned, indicate, however, that the improvement in renal function brought about by desoxycorticosterone is not maintained at a normal level over long periods of time despite adequate dosage of hormone, i.e., enough to maintain normal serum values for sodium and potassium.

The effect of desoxycorticosterone esters upon arterial blood pressure in patients is worthy of comment. The pressure gradually rises to normal in the course of 2 to 4 weeks of treatment, as it tends to do in patients treated with salt alone. This slow recovery stands out in contrast to the almost immediate effects upon water, electrolyte metabolism and renal function. In a number of instances, the blood pressure of patients treated with desoxycorticosterone esters has exceeded normal limits and has been observed to be 175/110, 160/92, 154/105 and 146/108 in different patients. The mechanism of this hypertension is not understood but a comparison of the effects of desoxycorticosterone and salt in one patient is of interest. In this patient, whose pressure reached 175/110 with desoxycorticosterone, crises with a fall in sodium and fall in pressure to 85/60 were induced on two occasions by the withdrawal of salt from the diet. When salt was given in doses of 15 grams daily

without any cortical hormone, the blood pressure rose to 160/100. At autopsy this patient was found to have marked renal arteriolar sclerosis and both adrenal glands were replaced by tuberculous masses. In this individual whose adrenal function was so seriously impaired that, without salt or desoxycorticosterone, he sank into profound hypoadrenalism, hypertension could be induced, in the presence of renal arteriolar disease, by the administration of either sodium chloride or desoxycorticosterone. Swingle⁵⁴ has recently suggested that the elevation of arterial pressure in adrenalectomized dogs treated with desoxycorticosterone results from an increase in arteriolar and capillary tone. In view of the fact that a similar effect on blood pressure may result from salt alone, the question must be raised whether this increase in pressure may not be more properly ascribed to an ion effect on the vessels than to direct hormone action.

The mechanism of pigmentation in Addison's disease remains obscure and the effect of desoxycorticosterone upon it is still equivocal. Thorn⁵⁵ has maintained that treatment with this steroid decreased pigmentation. We have felt that decrease in skin color might be ascribed entirely to rehydration and gain in weight. The recent disappearance of "ink spots" from the buccal mucous membrane in one of our patients treated for two and a half years, perhaps, tends to support the viewpoint of Thorn.

Early in the course of our experience⁵² it was found that whereas the subjective and objective benefits derived from treatment with desoxycorticosterone esters are impressive, this therapy is not devoid of danger. Indeed, five patients developed symptoms and signs of congestive heart failure including pulmonary congestion, elevation of venous pressure and cardiac dilatation as is shown in Fig. 6. The mechanism of this cardiac failure was not determined but did not appear to be directly correlated with the degree of increase in plasma volume, the height of the arterial pressure attained or the degree of depression of the serum potassium level.

Because of the development of this complication with large doses of desoxycorticosterone, it seemed appropriate to study^{56, 57} the effects of prolonged administration of this steroid on normal animals. For this purpose, a series of dogs was given 25 mg. of desoxycorticosterone acetate daily for a period of some weeks. Although we were unable to produce either edema or cardiac dilatation in these animals, nevertheless two striking abnormalities appeared with great regularity. The ani-



Fig. 6—The effect of desoxycorticosterone upon the heart of a patient with Addison's disease. At the left is the heart before treatment. At the right is the heart after treatment with excessive doses.

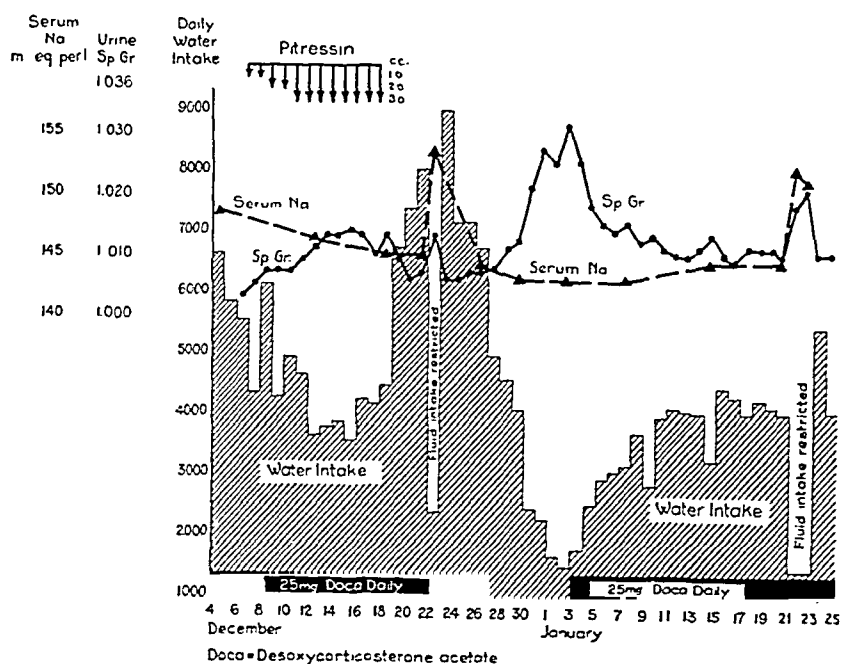


Fig. 7—"Diabetes insipidus" induced in a normal dog by daily injections of desoxycorticosterone. The urine output corresponded to water intake and the weight of the animal remained constant.

mals, in the course of 10 days, began to increase their water intake and output and gradually developed a diabetes insipidus-like syndrome. The degree of water drinking was increased by the addition of sodium chloride to the diet. The fluid intake increased from 500 cc., as a rule, to about 3-5 liters a day and the urine volume increased correspondingly. Part of the record of water-drinking of one dog is shown in Fig. 7. The water intake appeared to be slightly depressed by the injection of pitressin and this change was accompanied by an increase in the specific gravity of the urine. The restriction of fluid was associated with a sharp rise in serum sodium level. Unlike true diabetes insipidus, the restriction of fluid intake was associated with an increase in urine specific gravity. The "diabetes insipidus" was promptly terminated by the discontinuation of desoxycorticosterone injections. Thus, the urine specific gravity rose and the water turn-over dropped to normal, even though the sodium intake was kept at a constant level.

The second abnormality which developed in the normal dogs treated with desoxycorticosterone was a curious type of muscle weakness. This began to develop 4 to 5 weeks after the onset of treatment. In the early stages it appeared as intermittent periods of weakness. In these attacks it was impossible for the animals to raise their heads and weakness of the extremities, particularly the hind legs, was marked. These attacks of weakness usually occurred in the afternoon, possibly bearing a relation to the time of feeding, and would disappear by the following morning. In the course of about 10 days to 2 weeks, the weakness became progressively worse and more continuous. If not treated, the animals would finally succumb.

The blood serum of these animals developing "diabetes insipidus" and periodic muscle weakness showed an increase of 4 to 8 m.eq. per liter in sodium and a depression of potassium to about 2.5 m.eq. per liter.

It was found⁵⁸ that if the animals were given a 0.15 per cent solution of potassium chloride to drink instead of tap water, the development of muscle weakness did not occur, but no influence was observed upon the development of the "diabetes insipidus." The substitution of tap water for potassium chloride solution led to the appearance of intermittent muscle weakness in about 10 days. It was found that the administration of potassium chloride tended to prevent the decrease in serum potassium level, but had no influence on the elevated sodium concentration.

Analysis of the skeletal muscles of animals with severe weakness

EFFECT OF DOCA UPON THE CONCENTRATION OF SODIUM AND POTASSIUM IN DOG MUSCLE

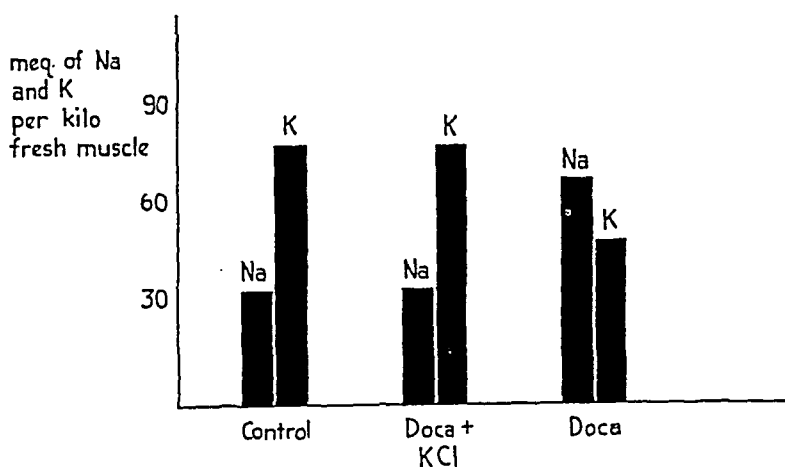


Fig. 8—The effect of desoxycorticosterone acetate upon the concentrations of sodium and potassium in the skeletal muscle in the dog. N.B. The addition of KCl to the drinking water inhibited the muscle changes but had no effect upon the "diabetes insipidus."

showed that they contained a large amount of sodium and less than the normal amount of potassium. Similar changes had been described by Darrow⁵⁹ in the muscles of rats treated with desoxycorticosterone. The increase in muscle sodium was found in our studies⁵⁸ to be prevented when potassium chloride was added to the drinking water as is shown in Fig. 8. Analysis of the muscles for nitrogen, chloride and water in paralyzed animals and animals protected with potassium chloride indicated no apparent change in the extracellular water jacket or so-called chloride space. This is demonstrated in Fig. 9. In Fig. 10 it is shown that the intracellular replacement of potassium by sodium appeared to be on an approximately 1 to 1 basis, an atom of sodium being gained for each atom of potassium lost.

In these studies it is clear that the "diabetes insipidus" could be correlated with an increase in sodium concentration in the serum and therefore in the extracellular fluid. This elevation in sodium level and the "diabetes insipidus" persisted regardless of potassium chloride administration. The muscle weakness, on the other hand, was associated with an increase in intracellular sodium. This change could be prevented by potassium chloride feeding even though the serum sodium concentration remained elevated. It thus seems preferable to speak of the effect

EFFECT OF DOCA UPON THE WATER, NITROGEN AND CHLORIDE CONTENT OF DOG MUSCLE

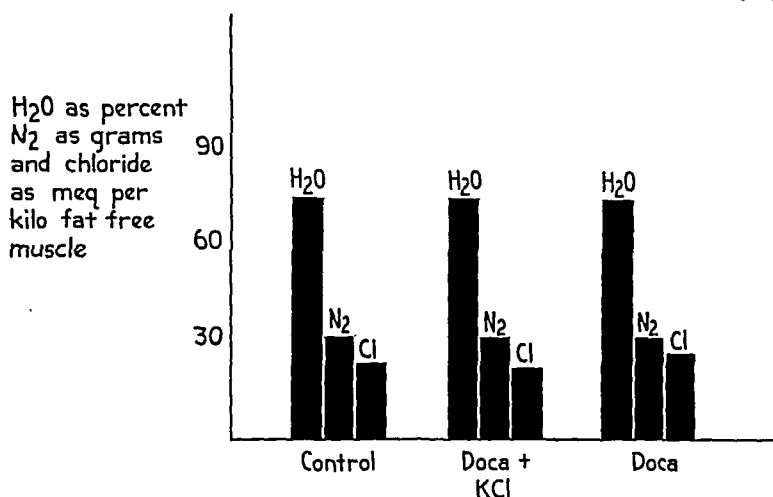


Fig. 9—Analyses of muscles of normal dogs receiving large doses of desoxycorticosterone yield no evidence of an increase in interstitial fluid, i.e., the "chloride-space."

EFFECT OF DOCA UPON THE CONCENTRATION OF INTRACELLULAR Na AND K

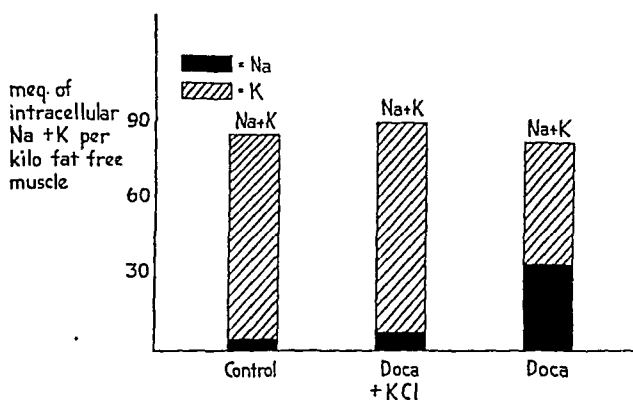


Fig. 10—The intracellular replacement of the K ion by the Na ion in muscles of normal dogs receiving desoxycorticosterone is on an approximately 1 to 1 basis. This replacement of K by Na is inhibited by the administration of KCl.

of desoxycorticosterone upon intracellular electrolytes in the normal dog as one in which potassium lost from the cells is *replaced* by sodium rather than one in which a high concentration of extracellular sodium in some way *displaces* intracellular potassium. In other words it appears that sodium goes into muscle cells only when potassium comes out. This view is consistent with the idea that desoxycorticosterone, by in-

creasing the renal excretion of potassium, lowers the serum potassium concentration and shifts the equilibrium between intracellular and extracellular potassium in the direction of an increased loss of potassium from the cells. Heppel's¹ observations on the increase in intracellular sodium in rats raised on a low potassium diet offer support for this interpretation. It seems clear therefore, that when the available supply of potassium is reduced either by reduction in intake or by excessive excretion sodium replaces the potassium which is lost from the muscle cells.

These effects of excessive doses of desoxycorticosterone in normal dogs bear some similarity to electrolyte disturbances observed first by Anderson⁶⁰ in the blood serum of patients suffering from Cushing's syndrome. In these patients, in whom tumor of the adrenal cortex is often present, there may be an elevation of serum sodium and depression of potassium. Whereas mild diabetes insipidus has been reported in these patients⁶¹ this has not been observed in the small group of cases studied by us. Furthermore, muscle biopsy carried out in three of our cases has not revealed the replacement of potassium by sodium seen in dogs treated with desoxycorticosterone. The muscle weakness of patients with Cushing's syndrome does not, therefore, appear to have the same chemical basis as does the intermittent paralysis of desoxycorticosterone treated dogs.

I have dealt at length with the action of desoxycorticosterone esters upon electrolyte metabolism. I should like now to consider briefly the effects of the various physiologically active steroids isolated from the adrenal cortex upon the interrelations of electrolyte behavior, life maintenance, carbohydrate metabolism and the capacity for muscular work. In general there appears to be a close parallelism between the effect of a steroid on sodium retention and on life maintenance. This is demonstrated by the fact that sodium salts in the absence of cortical hormone will sustain adrenalectomized dogs and rats. There is also an apparent correlation between the effects upon carbohydrate metabolism and upon work-capacity. Furthermore there appears to be a possible antagonism between these two groups of functions. Most of the studies devoted to the correlation of these various activities have had to be carried out on animals and are unfortunately limited in number because of the small quantities of those steroids so far isolated and because only desoxycorticosterone has been made available through its synthesis.

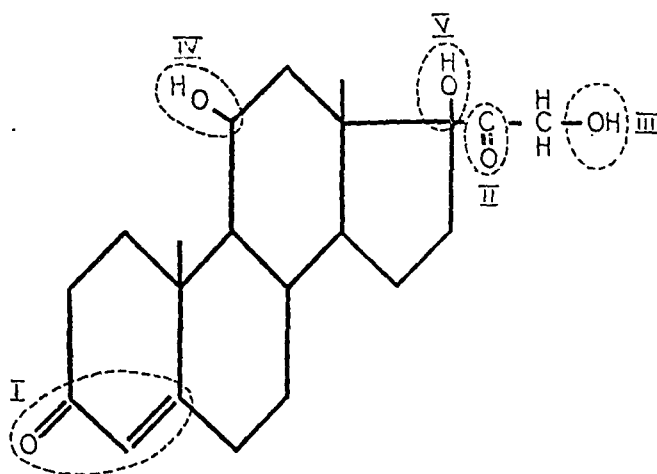


Fig. 11—I. Is essential for all known physiological activity. II. is essential for all known physiological activity. III. enhances sodium retention; necessary for carbohydrate activity. IV. (Either a hydroxyl or a carbonyl group.) In the presence of III, decreases sodium retention and increases carbohydrate activity. V. In the presence of III, and ? IV, increases carbohydrate activity and induces sodium excretion. This correlation of adrenal function and structure of various steroids is suggested by Thorn. (Reprinted with permission.)

The great advances in our understanding of carbohydrate activity have developed primarily from the studies of Britton and Sylvette,⁶² Kendall and his associates,^{28,63} C. N. H. Long⁶⁴ and from Thorn and his co-workers⁶⁵ in the past 10 years. The relation between the capacity for muscular work and the various cortical steroids has been clarified through the carefully controlled observations of Ingle.⁶⁶ It is established that desoxycorticosterone is the most potent of the isolated adrenal steroids in affecting sodium retention and life maintenance. Yet this steroid in man, as well as in the experimental animal, is virtually without effect upon carbohydrate metabolism or work-capacity, the latter being determined in adrenalectomized rats. Corticosterone has definite but less sodium-retaining effect in man⁶⁷ and animals⁵¹ than has desoxycorticosterone. On the other hand it has slight but demonstrable effect upon carbohydrate metabolism in man.^{65,67} In animals it has considerably greater effect upon carbohydrate metabolism and work-capacity than has desoxycorticosterone.

Very recently Thorn⁶⁸ has made a most important advance in our knowledge. He has shown that 17-hydroxycorticosterone and 11-dehy-

dro-17-hydroxycorticosterone (compound E of Kendall), the two steroids most active in their effects on carbohydrate metabolism and work-capacity, have no sodium retaining effect in the dog. Moreover they appeared to increase the excretion of the sodium ion. This fact is the more interesting since the effect of these steroids on life maintenance is indeed relatively small. On the basis of these observations, Thorn has presented a diagram (Fig. 11) in which he has attempted to correlate the relation between various physiological activities of the cortical steroids and their chemical structure.

Before closing I should like to mention evidence suggesting that adrenal cortical insufficiency may be associated with significant physiological disturbances other than those of electrolyte and carbohydrate metabolism. To what extent some of these changes may be primary and specific in nature and to what extent they are secondary to the recognized disturbances and make their appearance because the organism is "sick" is at times difficult to determine. For example, in our laboratory we have found that some degree of tetrabromophenol-sulfonephthalein retention was present in 12 of 16 patients with Addison's disease. This retention varied from 5 to 15 per cent at the end of one half hour and was not related to the severity of sodium loss. This constitutes but slight retention of the dye, but is more than is normally encountered. Similarly a mild depression of the basal metabolic rate is found in Addisonian patients as it is in adrenalectomized animals. Whether this results from a specific depression of thyroid activity from lack of adrenal hormone or whether it may possibly result from decreased blood flow or other causes is not known. The failure of glucose and fat absorption from the bowel of animals in adrenal insufficiency was thought by Verzar⁶⁹ to signify that a specific failure of phosphorylation existed in adrenal insufficiency. It was shown, however, by Althausen, Anderson and Stockholm⁷⁰ that the failure of absorption of glucose was dependent only upon dehydration and that administration of saline solution restored glucose absorption to normal. MacKay⁷¹ also found that fat is normally absorbed if salt solution is given to avoid dehydration.

In 1933 Swingle³⁸ and his coworkers first suggested the possibility that the adrenal cortex exerts an effect upon the capillaries and that loss of the adrenal cortex resulted, for this reason, in the state of shock. Since that time a large number of studies have been devoted to the possibility of a relation between the adrenal cortex and the cause and cure

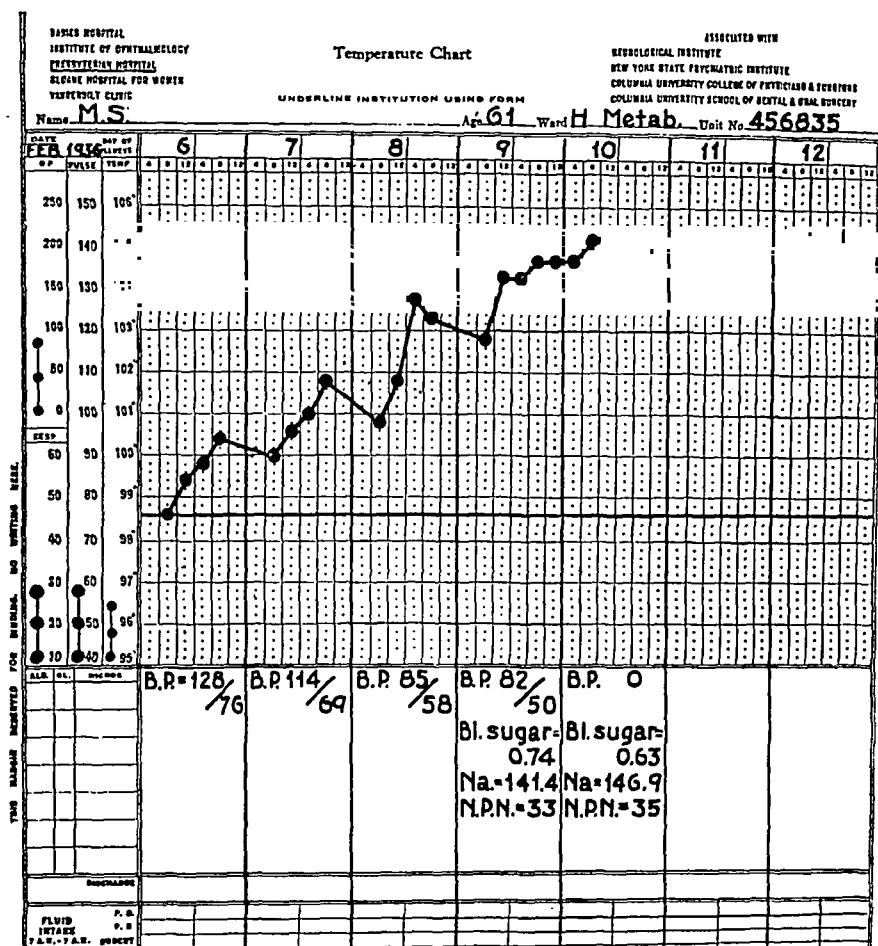


Fig. 12—A fatal adrenal crisis occurring without significant disturbance of the electrolyte pattern of the serum or of the blood sugar. No cause of death other than destruction of the adrenal glands was found post mortem.

of shock. This interest has been greatly augmented recently for obvious reasons, but no final answer can as yet be given. The evidence concerning the influence of adrenal cortical hormones in the treatment of experimental and clinical traumatic shock is at present controversial and not wholly convincing. Menkin's⁷² observation that the administration of cortical extract prevents the usual capillary dilatation following the injection of leukotaxine, however, is suggestive. The recent observation of Swingle⁵⁴ that plasma transfusion in a dog in adrenal insufficiency causes edema and collapse whereas this can be prevented if the dog is first treated with desoxycorticosterone or cortical extract also indicates a capillary disturbance in adrenal insufficiency.

We pointed out four years ago²⁹ that a certain number of patients

with Addison's disease die a typical Addisonian death, characterized by profound asthenia, falling blood pressure, a small or soft pulse and peripheral cyanosis but without the characteristic chemical changes in the blood serum. In these patients, the syndrome of shock may develop rapidly and without apparent relation to the state of the electrolyte and water metabolism or to the blood sugar level, but it is associated with a terminal rise in temperature which cannot be explained at autopsy (Fig. 12). Furthermore, in recent years, it has been found that these patients, at times, fail to respond to the administration of adequate therapy with desoxycorticosterone and potent cortical extract as judged by their effects on the water content of the blood plasma, the concentration of serum electrolytes and the blood sugar. It has been our impression that these patients die from a disturbance in vasomotor regulation, either peripheral or central in origin and that this is not consistently controlled by the cortical hormones now available.

In conclusion it may be stated that the adrenal cortex has been shown to exert an important influence upon the physiological activity of certain electrolytes and water as well as upon carbohydrate metabolism. Furthermore, through the chemical identification of a number of steroids isolated from the adrenal cortex an encouraging beginning has been made in the correlation of the chemical structure of these substances with certain physiological activities. It is to be hoped that with the further advance of our chemical knowledge of the hormones of the adrenal cortex that their effects upon capillary tone and permeability as well as upon cellular metabolic processes in general will be further elucidated.

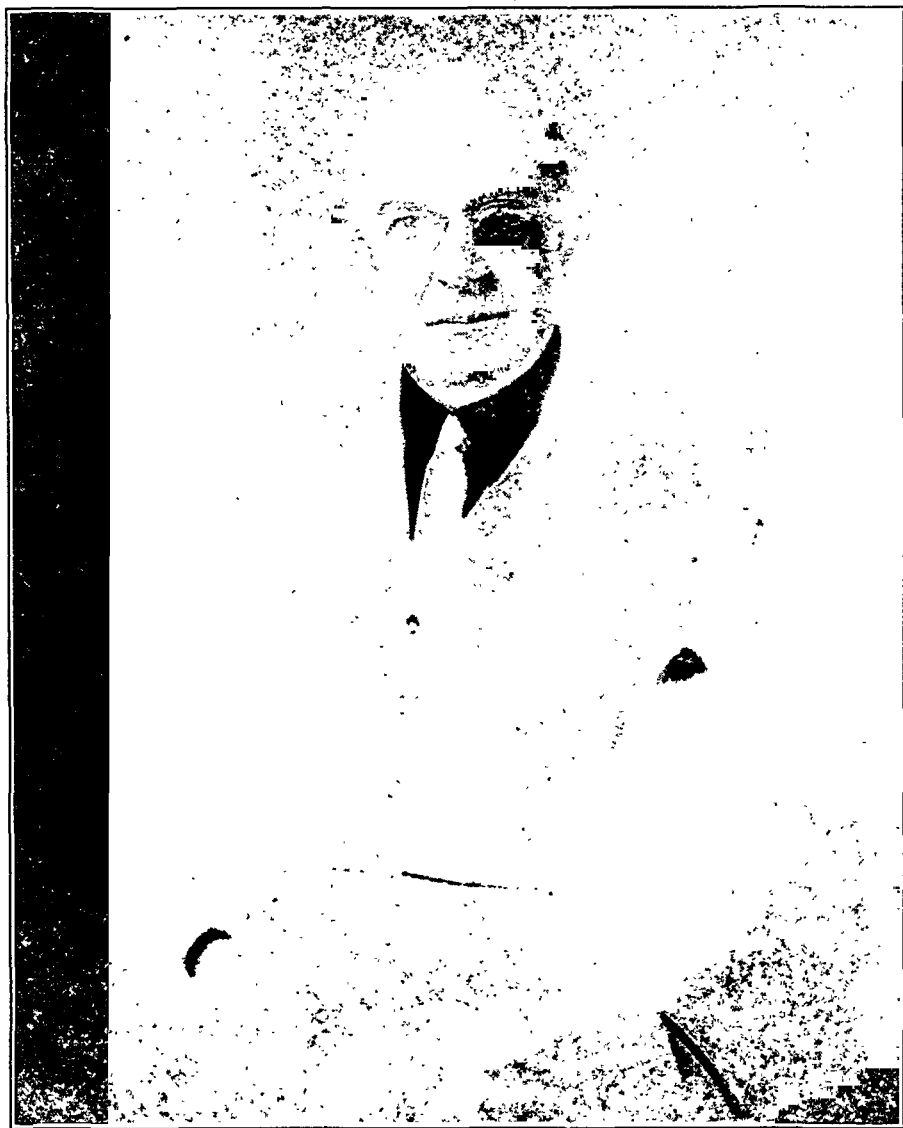
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WALTER LINDSAY NILES

1878-1942

WALTER LINDSAY NILES

AN APPRECIATION

IN the death of Walter Lindsay Niles The New York Academy of Medicine has suffered an irreplaceable loss. Dr. Niles was born on January 2, 1878 on one of the farms of the community known as "Niles Settlement," founded in 1808 in the Town of Lebanon, N. Y., by his great, great grandfather (Nahum Niles) and his sons, and there both his father, Isaac Newton Niles, and his mother, Harriet Lois Lindsay, were also born.

His paternal ancestor in America was John Niles who arrived from England on the ship Speedwell and settled in Dorchester, Massachusetts in 1634. His maternal ancestor came to this country from Scotland in 1645.

Dr. Niles was of the ninth generation descended from John Niles. This then is the foundation upon which his character was built. No wonder he possessed great courage, common sense to a high degree, a perfectly educated will and honesty of purpose. Virtue and genius were in his blood.

In his early boyhood he attended the district school in Lebanon. He graduated from the High School at Norwich, N. Y. in 1896 and in the autumn of that year entered the School of Civil Engineering, Cornell University, with the aid of a scholarship won in competitive examination.

With the death of his father in 1898, Dr. Niles decided not to complete his engineering course but to enter the school of medicine.

During his school-boy days, Walter Niles commanded the respect and affection of his companions and even his elders in the community recognized in him the leader and representative of his age group on any matter affecting policy. As an undergraduate in Cornell he rowed on the freshman crew squad and sang on the glee club. He was the chairman of a committee which published the "Songs of Cornell" and was a member of his senior banquet committee. He was a member of Sphinx Head, a senior honorary society, and of Savage Club.

After his graduation from medical school in 1902 he served two

years as a member of the intern staff of Bellevue Hospital. One of the attending physicians on the medical service at this time was the then Professor of Medicine at Cornell, Dr. Gilman Thompson, and it was he who persuaded Dr. Niles, after he had finished his internship in 1904, to remain in New York to take up the practice of medicine. From the day this decision was made down to the time of his death, he devoted himself to every phase of medical care and served humanity with great distinction to himself and to his profession.

Very shortly after the completion of his internship, he was appointed to the attending staff of Bellevue Hospital as an adjunct assistant attending physician. Later he became a consulting physician to this institution. He was also consulting physician to the Memorial Hospital, the New York Infirmary for Women and Children and the Southampton, Jamaica and Nassau Hospitals. He was an attending physician to the New York Hospital and a member of the Joint Administrative Board of The Society of the New York Hospital and Cornell University Medical College. He was professor of Clinical Medicine in the Medical College for many years. He was not only an inspiring teacher but his capacity for organization led to his being appointed Dean of the College in 1919, an office he retained for nine years. Indeed, due to the illness of Dean Ladd, he was serving as acting Dean at the time of his death.

In 1908 Dr. Niles was elected a Fellow of The New York Academy of Medicine. During his more than thirty years of Fellowship he served on the following committees of the Academy: Admissions, Public Health Relations, Medical Education, Problems of Medical Practice, Professional Standards, Fund Raising and finally he was Chairman of its Board of Trustees and the Executive Committee of this Board.

He declined an invitation to become President of The New York Academy of Medicine because other duties to which he was already pledged would not give him sufficient time to do this office full justice.

Dr. Niles was a member of numerous scientific societies and organizations among which were: The Association of American Physicians, The American Climatological and Clinical Association, The Harvey Society and The Practitioners Society. His clubs were The Links, Century Association, Cornell, National Golf Links, Shinnecock Hills Golf Club, Meadow Club (Southampton), Piping Rock and Deepdale.

In the very early days of the first World War Dr. Niles received

a telegram from Dr. Theodore Janeway offering him a commission as major in the United States Army Service Medical Corps.

He was persuaded, against his own wishes and desires, that he could best serve his country by retaining his teaching post in the medical school. Once he was convinced of this he made the sacrifice cheerfully.

Dr. Niles was as successful in private practice as he was in every other phase of medicine with which he was identified. People liked him and he liked people. I heard one man give the following reason for his success in the practice of medicine, "People felt safe in his hands." That statement is substantial evidence that his good judgement and wisdom were associated with high character, objective, straight thinking and complete honesty, blended with kindness, gentleness, patience and tolerance.

One of the reasons why he did so many things well was that he possessed the rare quality of being able to do one thing at a time to the exclusion of all else. When he played, and he loved to play, he concentrated on play. When he worked, all his thought was centered on the single problem in hand.

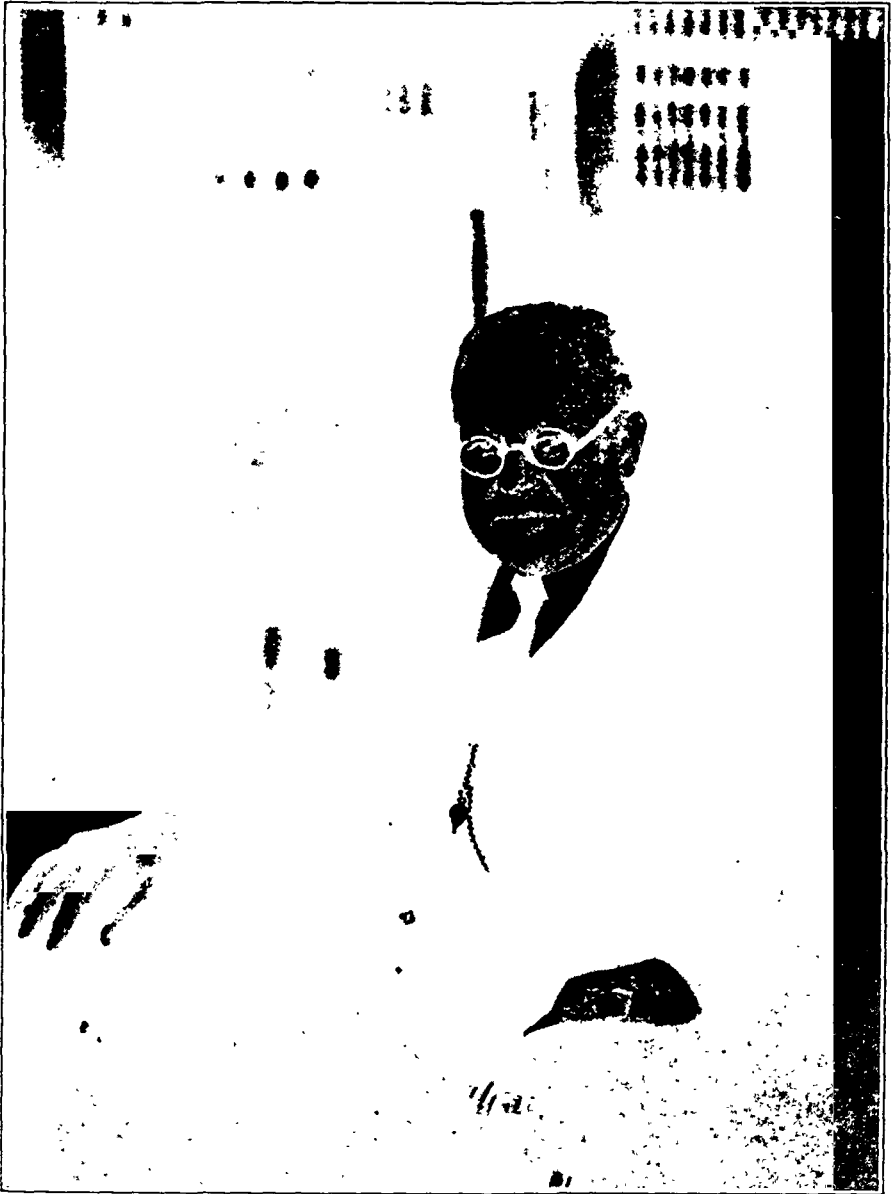
On May 20th, 1908 he married Louise Vezin, daughter of Charles Vezin and Adah Delamater.

There were four children of this marriage: John Lindsay Niles, Charles Lindsay Niles, Harriet Lindsay Niles—now Mrs. Edward A. Hurd, Jr.—and Nelson Robinson Niles. The latter two children and his wife survive him.

Schiller said: "Genuine morality is preserved only in the school of adversity." There was plenty of adversity in Walter Niles' life and in every instance when he was compelled to face ill fortune, he did so with a decision and nobility that was characteristic of him. He refused to be crushed. He carried on with a fine sense of his obligation to the world. Whatever concerned humanity concerned him. He refused to permit Fate to destroy him until she did a complete job of it. He loved life but only a life capable of doing things.

His death came with the suddenness he would have wished and it came at the very zenith of his career.

MALCOLM GOODRIDGE.



SAMUEL W. LAMBERT

1859-1942

SAMUEL W. LAMBERT

DR. SAMUEL W. LAMBERT died February 9th, 1942 in his eighty-third year. His life was one of action and accomplishment. A wonderfully successful practitioner, an educator, bibliophile, fisherman and delightful companion, he gave all he had, and that was much.

His father, Dr. Edward W. Lambert said all he could give his children, of whom eight grew to maturity, was a good education. Dr. Lambert had that, and made the most of it. He received his A.B. from Yale in 1880, and his Ph.B. after two additional years at the Sheffield Scientific School in preparation for his medical studies. At P. & S. his preceptor was Dr. H. B. Sands, and he was graduated in 1885 with Harsen honors. He received an appointment at Bellevue and then studied abroad for two years. He started practice in New York, in 1889.

From the very beginning he was much interested in Medical Education. Impressed with the woeful lack of practical obstetrical teaching in this country, with Dr. James W. Markoe, and with the backing of his father, Dr. Thomas M. Markoe, Dr. William T. Lusk, and Dr. William M. Polk, he organized the New York Midwifery Dispensary in Broome Street, in 1890. Students were enrolled, and after preliminary instruction, under supervision they delivered women in their tenement homes. During its two years of independent existence, over 300 students took the course. So successful and valuable was this work that the Society of the Lying-In Hospital was roused from a long period of inactivity. Originally organized as a hospital, it had degenerated into an eleemosynary organization giving deserving women \$25 to pay for their confinement. The Trustees founded a hospital at 17th Street and Second Avenue, which opened in 1895. They took over the Broome Street organization as its out-patient department in 1892. Dr. Lambert and Dr. Markoe were therefore responsible for starting a service well-remembered by the older members of the profession, and which did much in developing medical education. Dr. Lambert served on the Attending Staff of the Lying-In for twelve years.

In 1904 he became Dean of the College of Physicians and Surgeons, and for fifteen years devoted his energies to improving the scope and

character of the teaching in that organization, in spite of much opposition. He brought about its union with the Presbyterian Hospital and formed plans, never entirely carried out as he planned them, for the development of a teaching hospital, in which emphasis was laid on the teaching of practical medicine to every student in the College through bedside experience. Retiring in 1919, he was made its first Dean Emeritus.

As a practitioner of Medicine, Dr. Lambert was eminently successful, building up a large private and, later, consulting practice. Always abreast of the times, he was wise and resourceful, never forgetting the comfort of his patients in his interest in their diseases. He was one of that fast diminishing number of physicians who treat *patients* and not *cases*. His sympathy for the suffering or sorrowing was very real. His patients were devoted to him and became his fast friends and admirers. As a consultant, he was considerate and helpful to younger men, and when in difficulty they frequently called on him for help. They not only respected and admired him, but to many, he was "Dr. Sam."

Dr. Lambert was connected with many hospitals and medical societies. The long list need not be repeated here. In addition to the Lying-In, he was at various times Attending Physician to the Nursery and Childs, New York and St. Luke's. With the latter he was actively connected for twenty-three years. He was Consulting Physician to more than twenty institutions. The Medical Societies to which he belonged, both national and local, were also many—the Association of American Physicians, the College of Physicians, the Practitioners and others. Just before Sir William Osler left this country, he invited a small group of physicians and surgeons to form with him the Interurban Medical Club. Dr. Lambert was one of them.

Although elected a Fellow of the Academy in 1891, his deep interest in it was not shown until he became President in 1927. He did much in those important years to develop its ever-widening sphere of usefulness to its members and to the public. His valuable services continued after his term of office was over. He was particularly interested in the Library, for books were one of his hobbies. The assembling of the collections for the Rare Book Room and its stacks, including the purchase of the Streeter Collection, was largely due to his efforts and enthusiasm. Always interested in Vesalius and his Anatomy, he stimulated a further search in Munich for the original woodblocks, resulting

in the discovery of many which had been lost up to that time. He collected the money necessary to issue an Atlas containing all the original illustrations, beautifully printed on modern paper by modern methods. He was a very active member of the Library Committee from 1932 to 1941, when he was made Consultant. His interest and support never flagged. He was made a Benefactor of the Academy in 1941.

Dr. Lambert's life was a broad one. He played as actively as he worked—when he had the time. An enthusiastic bibliophile, he collected the books he loved, and he knew them from cover to cover. He was a regular attendant at the meetings of the Grolier and Charaka Clubs. To hear him talk about his beloved volumes was a rare treat. His little book "When Mr. Pickwick went Fishing" illustrates his wide knowledge of his hobby. An ardent fisherman himself, his collection of editions of Isaac Walton's "Compleat Angler" and Cotton's works is a notable one and was probably his most treasured possession. He collected them for many years, and each new acquisition gave him great joy. He belonged to several fishing clubs in this country and in Canada.

Dr. Lambert was a loyal friend, and a companion who from the store of his exceptional memory of men and events, told anecdotes, apt and to the point, tinged with rare humor, demolishing chicanery and fraud which he hated.

He led an active, constructive, worth while life. He will be sadly missed.

PHILIP VAN INGEN.

DEATHS OF FELLOWS

LAMBERT, SAMUEL WALDRON: 101 East 72 Street, New York City; born in New York City, June 18, 1859; died in New York City, February 9, 1942; received from Yale University the degree of A.B. in 1880, Ph.B. in 1882, A.M. in 1905; and from Columbia University the degree of D.Sc. in 1921; graduated in medicine from the College of Physicians and Surgeons in 1885; elected a Fellow of the Academy February 5, 1891; served the Academy as its President from 1927 to 1929, as a member of the Board of Trustees from 1929 to 1939, as a member of the Committee on Public Health Relations from 1929 to 1936, as a member of the Committee on Library from 1932 to 1942 and as consultant to that Committee from January 1942 to the time of his death.

Dr. Lambert was dean emeritus of the College of Physicians and Surgeons, Columbia University, having served as its dean from 1904 to 1919. From 1903 to 1919 he was professor of clinical medicine at that institution. He was consulting physician to St. Luke's, New York, Presbyterian, St. Vincent's, Neurological Institute, New York Orthopedic, Ruptured and Crippled and St. John's, Riverside and Yonkers Hospitals. He was a member of the Board of Trustees of Roosevelt Hospital (1904-19), a Fellow of the American College of Physicians, a member of the Association of American Physicians, the American Gastro-Enterological Association and the State and County Medical Societies.

WALSH, JAMES JOSEPH: 344 West 72 Street, New York City; born in Archbald, Penn-

sylvania, April 12, 1865; died in New York City, March 1, 1942; received the degree of A.M. from Fordham University in 1885, Ph.D. in 1889, LL.D. from Georgetown University in 1901, and Sc.D. from Notre Dame in 1909; graduated in medicine from the University of Pennsylvania Medical School in 1895; elected a Fellow of the Academy March 3, 1904.

Dr. Walsh became an instructor in medicine in 1900 at the New York Polyclinic School of Medicine and adjunct professor in 1904. The latter position he resigned in 1907 to become the acting dean and professor of physiological psychology at Cathedral College. He was consulting physician to Gabriels Sanatorium and St. Vincent's Hospital, a Fellow of the American Medical Association, a member of the American Association for the Advancement of Science, and a member of the State and County Medical Societies.

Dr. Walsh was a prolific writer on medical, scientific and religious subjects and established the Fordham University Press which published his articles on the history of medicine and related subjects.

WITT, DAN HITER: 71 East 71 Street, New York City; born in Charlottesville, Virginia, May 20, 1890; died in New York City, February 15, 1942; graduated in medicine from the University of Virginia in 1914; elected a Fellow of the Academy October 2, 1924.

Dr. Witt was instructor in medicine at Cornell University Medical College, assistant visiting physician to the New York Hospital and consultant visiting physician to the Manhattan Eye, Ear and Throat Hospital. He was a diplomate of the American Board of Internal Medicine, a Fellow of the American Medical Association and a member of the State and County Medical Societies.

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BULLETIN OF
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MAY 1942

SOME CHEMICAL CHANGES IN THE
MYOCARDIUM ACCOMPANYING
HEART FAILURE *

VICTOR C. MYERS

Professor of Biochemistry, School of Medicine, Western Reserve University

THE normal function of the heart is dependent upon a recurrent series of beautifully coördinated physical and chemical processes. Obviously a break anywhere in this chain of processes affects the action of the heart as a whole. Much attention has been given to the pathology of the heart and its effect, not only upon the circulation of the blood, but also upon the blood supply and nutrition of the heart itself. Two of my Cleveland colleagues^{1,2} have recently addressed the Academy upon topics dealing with this general subject. It is evident that the normal function of the heart cannot be maintained without an adequate blood supply, to furnish food materials, including oxygen, for the energy of the heart's action. It is equally evident that the heart is dependent upon a properly functioning chemical mechanism by which this material can be converted into mechanical energy. It is this last phase of the subject that I wish to discuss.

With the discovery of phosphocreatine by Fiske and Subbarow³ in

* Presented at a joint meeting of the New York Heart Association and the Section on Medicine of The New York Academy of Medicine, January 20, 1942.

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With the discovery of phosphocreatine by Fiske and Subbarow³ in

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1927, and the subsequent discovery of adenosinetriphosphate, our theories regarding the energetics of muscular activity have been entirely changed. Without entering into a theoretical discussion, it would appear that compounds of phosphorus, phosphocreatine and adenosinetriphosphate in particular, are intermediaries in the transfer of chemical energy to the mechanical energy of the heart beat. It seems probable that these organic phosphoric acid compounds exist as potassium salts,⁴ and would thus account for most of the intracellular potassium. If the above premises are correct, the concentration of these compounds in the myocardium should serve as an index of the potential capacity of the heart for work.

Phosphocreatine is such a labile compound that it is impossible to determine it in the human heart obtained at autopsy. However, variations in creatine are probably equally significant. It should therefore be of interest to study the changes which occur in the creatine, purine nitrogen, phosphorus and potassium of the myocardium in disease. In addition, adequate evaluation of these data might be difficult without information on the water, sodium chloride, lipid and collagen content of the tissue.

With this background a series of studies on human hearts obtained at autopsy was begun in our laboratory in cooperation with the Department of Pathology more than ten years ago. Any success that may have been achieved has been due largely to the work of Linegar and Mangun of our department, to the cooperation of Seecof, Frost, Reichle and Strauss of the Department of Pathology, and to the financial assistance of the Josiah Macy, Jr. Foundation.

Although we were apparently the first in this country to undertake studies on the heart involving creatine⁵ we were slow in reporting our findings, and almost simultaneously and independently Cowan⁶ in Iowa City, and shortly afterwards Herrmann and his co-workers⁷ in Galveston reported creatine observations on the heart in agreement with our own. Herrmann in particular has vigorously attacked the problem, employing both animal and human material.

About the time our studies were undertaken the Vanderbilt University medical group attacked the problem of congestive heart failure from the standpoint of potassium. Calhoun, Cullen, Clarke and Harrison⁸ concluded one of their early papers with the statement: "It is believed that overwork causes loss of potassium from heart muscle and

TABLE I

AVERAGE DATA ON HEARTS OF THIRTEEN NORMAL HUMAN SUBJECTS
(mg. per 100 gm. of wet tissue)

| <i>Constituent</i> | <i>Left ventricle</i> | <i>Right ventricle</i> | <i>Voluntary muscle</i> |
|--------------------|---------------------------|----------------------------|-----------------------------|
| Creatine | 203 | 165 | 443 |
| Phosphorus | 194 | 160 | 201 |
| Potassium | 285 | 219 | 328 |
| Water | 80.8 | 82.3 | 76.2 |
| Fat | 0.35 | 1.28 | 1.68 |

that this loss is one of the predisposing factors to cardiac fatigue and failure." This statement is interesting and apparently correct, but appeared to us to be only part of a much larger chemical picture, involving creatine, phosphoric acid and adenosinetriphosphate.

Several brief statements may help in orientation. Creatine is present in heart muscle in about half the concentration it attains in skeletal muscle. Phosphocreatine has been reported by various investigators as present in concentrations from one-tenth to one-third that of skeletal muscle. Its lower concentration in heart muscle than in skeletal muscle cannot be attributed to a difference in the amount of the intracellular phase, since there is a sharp decrease in the ratio of creatine to potassium. The distribution of phosphorus compounds is likewise greatly different from that of skeletal muscle. While the total phosphorus of the heart is about the same as that of skeletal muscle, a much greater part is present in the acid-insoluble fraction, most of which is phospholipid. The acid-soluble fraction is accordingly less, and this difference may be traced largely to the lower phosphocreatine content of the heart.

When we began our study we were inclined to believe that the averages for our relatively large pathological series, covering a considerable range of values, would furnish figures not far from normal and adequate controls. This was nearly correct in the case of the myocardium, but not in the case of the voluntary muscle. If our theories regarding the function of phosphocreatine are correct, the creatine level in the myocardium must be reasonably maintained if heart failure is to be prevented. To secure more adequate control data hearts from 13 indi-

viduals dying accidental deaths were analyzed.⁹ Average data are presented in Table I. As will be noted the creatine, phosphorus and potassium are appreciably higher in the left than in the right ventricle. In the beginning we were inclined to attach special significance to this.⁵ It will be observed, however, that the water and fat are appreciably higher in the right ventricle. This also appears to be true for the connective tissue content.¹⁰ When allowance is made for the difference in the extracellular water, the fat and connective tissue, the difference between the ventricles is relatively small.

At this point it may be well to ask if the changes observed in the wet muscle of pathological hearts may not be due primarily to changes in water, connective tissue and fat. Wilkins and Cullen¹¹ have shown that in persons dying from congestive heart failure there is an increase in the water content of both ventricles, but especially the right ventricle. As might be expected this increase in water is accompanied by an increase in the sodium content, obviously in the form of sodium chloride. Recalculation of our figures on the basis of water and fat free tissue did not eliminate the very definite changes which occur in heart failure. On this account we have continued to record our findings on the basis of the wet tissue, since this is the condition in which the heart functions.

Since creatine appears to us to loom large in point of quantity and significance in heart failure, it will be well to call attention to several outside factors which exert some influence on the creatine content of the myocardium. Probably the most important of these are factors affecting the metabolism of creatine and the elimination of creatinine, which are reflected in the creatine content of voluntary muscle. Whereas the creatine content of voluntary muscle averages about 400 mg. per 100 gm. of fresh tissue in miscellaneous pathological conditions, it is definitely higher in strictly normal individuals, namely 443 mg. In uremia and fevers the creatine values tend to be elevated and range from 400 to 560 mg., while in such conditions as carcinoma and diabetes the concentration is definitely lowered—may reach 300 mg. The retention of creatinine no doubt accounts for the high creatine values observed in voluntary muscle in uremia. Hyperthermia is known to greatly increase the urinary excretion of creatinine and the relatively high creatine values found in fevers are probably explained in part at least by the whipping-up of creatine-creatinine metabolism. On the other

hand, the very low values found in diabetes may find explanation in the disturbance of carbohydrate metabolism.

In studying our data¹² on the creatine content of the left and right ventricle in comparison with the voluntary muscle, it was observed that the high values for the creatine of voluntary muscle in uremia and pneumonia were accompanied by correspondingly high values in the left ventricle, and in the right ventricle in uremia, but not in pneumonia. In diabetes, on the other hand, the creatine of the left ventricle is only slightly lowered, despite the marked fall in the voluntary muscle, suggesting that the creatine level of the heart muscle must be maintained if the heart is to function.

To secure further information on the influence on the myocardium of factors which elevate the creatine content of voluntary muscle, the data¹² were rearranged and grouped on the basis of the creatine content of voluntary muscle. It was found that as long as the creatine concentration of the voluntary muscle did not exceed about 425 mg. there was no elevating influence on the creatine content of the myocardium. When it exceeded this level, however, there was a definitely elevating effect on the creatine concentration of the left ventricle, although the values in the right ventricle remained essentially normal.

Cardiac Hypertrophy. The question of the effect of cardiac hypertrophy upon the chemical composition of the human heart is of importance both as a phenomenon in itself and in relation to myocardial failure. It would appear that cardiac hypertrophy is intimately associated with failure and may possibly be the principal factor in bringing about an eventual breakdown in the metabolic transfer between the blood and muscle required to keep pace with the increased demands upon the energy output. Wearn and his co-workers² have shown that as a result of the increase in diameter of the muscle fibers in hypertrophy there is a decrease in the number of capillaries per square millimeter of heart muscle. This ultimately leads to a considerable increase in the radial distance the metabolites must diffuse from each capillary, a situation which may conceivably lead to decreased nutrition and anoxia of the muscle fibers.

It is difficult to obtain entirely satisfactory information on the effect of hypertrophy on the chemical composition of the human heart because of the variability of the findings and the influence of other factors. Cowan⁶ observed that in hearts with hypertrophy the average

TABLE II

THE RELATION BETWEEN HEART WEIGHTS AND CONCENTRATION OF
CREATINE, PHOSPHORUS AND POTASSIUM
(EXCLUSIVE OF NITROGEN RETENTION CASES)
(mg. per 100 gm. of wet tissue)

| Group | Number of Cases | Weight of Hearts (gm.) | LEFT VENTRICLE | | | RIGHT VENTRICLE | | |
|---------|--------------------|---------------------------|----------------|-----|-----|-----------------|-----|-----|
| | | | Creatine | P | K | Creatine | P | K |
| I | 4 | 200-230 | 213 | 201 | 299 | 182 | 183 | 242 |
| II | 5 | 250-275 | 244 | 195 | 306 | 191 | 162 | 241 |
| III | 7 | 300-350 | 210 | 189 | 269 | 179 | 148 | 212 |
| IV | 9 | 375-450 | 196 | 181 | 271 | 152 | 145 | 195 |
| V | 7 | 450-530 | 177 | 178 | 265 | 129 | 141 | 192 |
| VI | 8 | 550-650 | 152 | 168 | 232 | 126 | 142 | 191 |
| VII | 4 | 650-825 | 140 | 184 | 213 | 110 | 140 | 172 |
| Normals | 13 | 275-500 | 203 | 194 | 285 | 165 | 160 | 219 |

creatinine concentration was slightly higher than in hearts without hypertrophy, but did not regard the difference as significant. In experimental studies in the rabbit Herrmann and his co-workers¹³ found that slight hypertrophy resulted in a definite rise in the creatine concentration which was somewhat more marked in the left than in the right ventricle. With more definite hypertrophy the creatine concentration dropped to considerably below the normal level in the left ventricle and to about the normal level in the right ventricle. It is of some interest that digitalized hearts showed a slight increase in creatine concentration.

In work carried out on human and animal hearts in our laboratory we have persistently noted a tendency toward higher creatine, phosphorus and potassium values with increases in heart weight. These differences, however, have been relatively small and of such magnitude as might be expected from variations in the amount of the intracellular phase in the myocardium. In an effort to ascertain the relation between heart weight and creatine content throughout the normal and pathological range we charted the data on 195 cases arranged according to heart weight.¹⁴ The findings may be summarized with the statement that at birth there is little difference in the creatine concentration of

TABLE III

AVERAGE CREATINE, PHOSPHORUS AND POTASSIUM CONCENTRATIONS IN CARDIAC MUSCLE IN MYOCARDIAL INSUFFICIENCY, COMPARED WITH OTHER PATHOLOGICAL CONDITIONS AND THE NORMAL
(mg. per 100 gm. of wet tissue)

| Condition | No. of Cases | LEFT VENTRICLE | | | RIGHT VENTRICLE | | |
|-----------------------------------|--------------|----------------|-----|-----|-----------------|-----|-----|
| | | Creatine | P | K | Creatine | P | K |
| Myocardial insufficiency | 17 | 146 | 169 | 232 | 112 | 135 | 178 |
| Miscellaneous cardiac involvement | 20 | 190 | 185 | 259 | 149 | 148 | 195 |
| Cor pulmonale | 4 | 217 | 186 | 271 | 136 | 132 | 166 |
| Diabetes mellitus | 3 | 200 | 197 | 272 | 126 | 144 | 194 |
| Uremia without heart failure | 11 | 246 | 199 | 286 | 182 | 153 | 205 |
| Normals | 13 | 203 | 194 | 285 | 165 | 160 | 219 |

the muscle of the two ventricles. After birth the creatine concentration rises rapidly in the left ventricle, although the rise in the right ventricle is slight. Creatine reaches a maximum in the left ventricle in the 50 to 150 gm. hearts, in the right ventricle in the 150 to 250 gm. hearts, maintains its highest level up to 350 gm., and then begins to fall, reaching its lowest level in the group of adult hearts weighing over 650 gm.

To rule out a factor which, as already noted, exerts a pronounced elevating influence on the level of creatine in the heart, namely nitrogen retention with its accompanying retention of creatinine and creatine, a table was prepared from data on 44 autopsy cases covering the range of heart weights but excluding all cases with nitrogen retention. It will be observed in Table II that with the first increments in heart weight there is a quite definite elevation not only of creatine in both ventricles but also of phosphorus and potassium. However, with further increments in heart weight all the values begin to fall and decline with each increment in heart weight, the final values being 20 to 35 per cent below the normal. Obviously the incidence of heart failure increases progressively with each increment of heart weight. It should be noted, however, that relatively high creatine values were frequently observed throughout the range of heart weights, indicating that hypertrophy itself does not necessarily limit the saturation level of the muscle.

Myocardial Insufficiency. The chemical changes which occur in the

myocardium in heart failure appear especially significant. Average data on 17 cases¹⁵ of myocardial failure are recorded in Table III, and similar data on cases classified as miscellaneous cardiac involvement, cor pulmonale, diabetes mellitus, uremia and normals for comparison. Only those patients whose condition was clinically diagnosed as myocardial insufficiency and who showed evidence of progressive decompensation with hyperemia of the internal organs and edema of the extremities, were included in this group of seventeen cases. Patients with less distinct signs of myocardial insufficiency, as well as those with nitrogen retention, were classified separately. As will be observed the average concentrations of creatine, phosphorus and potassium were decreased in both ventricles of the heart. In every case the creatine content of the left ventricle was below the normal level, varying from 16 to 52 per cent below the normal. The concentration of phosphorus was likewise lowered, but to a less degree, in all but 2 of the individual cases. The potassium also decreased in all but 2 cases, the average percentage decrease being somewhat more than that for phosphorus and less than that for creatine. Similarly lowered values are recorded for the right ventricle. It should probably be noted that in this series of cases with myocardial failure there was also a definite reduction in the creatine content of the voluntary muscle (average of 349 mg.), probably due in part to long enforced inactivity.

In attempting to interpret the losses in creatine, phosphorus and potassium which occurred in these cases of myocardial insufficiency, it appeared helpful to consider not only the percentage loss, but also the loss in relation to the molecule, dipotassium phosphocreatine. If the observed decreases were due chiefly to dilution of the active muscle tissue with water, fat or connective tissue, one might anticipate that the whole of the creatine, phosphorus and potassium would be affected. The net result would be that a decrease of 10 per cent, for example, in the creatine would be accompanied by a decrease of 10 per cent in the phosphorus and potassium. On the other hand, if the changes observed were due largely to a breakdown of the phosphocreatine mechanism, only that part of the phosphorus and potassium directly associated with the creatine might be expected to be lost.

When the data were calculated in terms of percentage decrease in the three constituents, and in terms of loss of millimoles per kilogram it was apparent that tissue dilution was not the important factor in-

TABLE IV

AVERAGE ADENINE (CALCULATED FROM OXY-PURINE NITROGEN),
CREATINE AND TOTAL ACID-SOLUBLE PHOSPHORUS CONTENT OF
HUMAN CARDIAC MUSCLE IN HEART FAILURE AND
OTHER CONDITIONS
(mg. per 100 gm. of wet tissue)

| | No. of Cases | LEFT VENTRICLE | | | RIGHT VENTRICLE | | |
|---------------|-----------------|----------------|----------|---------|-----------------|----------|---------|
| | | Adenine | Creatine | T A S P | Adenine | Creatine | T A S P |
| Entire Series | 24 | 86 | 205 | 106 | 54 | 153 | 74 |
| Heart Failure | 6 | 72 | 161 | 91 | 54 | 128 | 67 |
| Tuberculosis | 5 | 87 | 225 | 117 | 56 | 162 | 78 |
| Pneumonia | 8 | 90 | 222 | 110 | 48 | 160 | 75 |
| Miscellaneous | 5 | 91 | 211 | 107 | 63 | 161 | 78 |

volved, since there was no correlation between the percentage decreases of the three constituents in either ventricle. Calculations were then made on the assumption of the loss of the components of dipotassium phosphocreatine. Taking the loss of 4 mols of creatine as the standard of reference, one would expect a loss of 4 mols of phosphorus and 8 mols of potassium. The actual loss of phosphorus and potassium was found to exceed that of creatine.¹⁵ This fact is suggestive of a loss of adenosine-triphosphate, which would be in harmony with the findings of Burns and Cruickshank¹⁶ that this compound may break down in the heart under a variety of experimental conditions.

Recently we¹⁷ have put this question to experimental test as shown in Table IV. In a series of twenty-four human hearts, including six cases of congestive heart failure, we have carried out purine determinations in addition to determinations of creatine and total acid-soluble phosphorus. The nitrogen of the purines convertible to oxypurines was determined, and from this adenine was calculated. It will be observed that in heart failure the left ventricle shows a decrease in this purine fraction along with the decrease in creatine and total acid-soluble phosphorus. This fall does not appear to occur in the right ventricle. It should perhaps be noted that there does appear to be a drop in the adenine of the right heart in pneumonia. From the above it would seem that adenosinetriphosphate probably accounts for the major part of the phosphorus and potassium loss not accounted for by the creatine. There-

fore it does not appear probable that extensive changes occur in organic compounds of phosphorus other than phosphocreatine and adenosine-triphosphate.

Our series of cases has included only one case of coronary failure (thrombosis). Samples taken from areas that were not infarcted gave values within the normal range. Herrmann and Decherd¹⁸ have made creatine determinations in a number of such cases, cases that were presumably less acute than our single case, and observed a marked reduction of creatine in the infarcted areas, and a considerable reduction in the uninfarcted areas. In our cases of miscellaneous cardiac involvement (Table III) the average values are only moderately reduced. Data are also included in Table III on 4 cases of right-sided heart failure (cor pulmonale), showing comparatively low values in the right ventricle. While the heart fails as a unit it is evident that the right ventricle may show chemical evidence of failure without similar changes occurring in the left ventricle. The table likewise includes data on 3 cases of diabetes mellitus. Here too the findings for the left ventricle are essentially normal, but in the right ventricle the concentrations of all three constituents, especially the creatine, are reduced. It is interesting to note that in uremia essentially all the values for creatine, phosphorus and potassium are above normal, or normal, in the left ventricle and right ventricle (also in the voluntary muscle), although the greatest increase is in the creatine. In our earlier study¹² which included a slightly smaller number of cases we observed that in uremia without heart failure the creatine values were markedly increased, whereas in uremia with heart failure they were reduced. At the time we suggested that the high creatine values in uremia without heart failure might explain why the heart did not fail in these cases. This is an interesting question which requires further study. The fact that in uremia there is a tendency towards elevation of phosphorus and potassium as well as creatine suggests the possibility that the extra creatine may be retained as the potassium salt of phosphocreatine. Whether or not this might exert a beneficial effect on the heart by increasing the energy and base reserve of the myocardium is an interesting speculation.

It is obvious that while the most important fundamental chemical changes occurring in the myocardium in heart failure are probably indicated by the average values recorded in the tables and already discussed, many interesting and important points regarding the individual cases are

covered up by this procedure. For example, in many instances the changes are more pronounced in one ventricle than in the other. Comment on this would require discussion of individual cases, or small groups of cases, which is beyond the scope of the present paper.

Discussion. It is interesting to note that the chemical approach to the problem of heart failure was first attacked with the determination of creatine in the myocardium by Constabel¹⁹ in 1921 and that to date no other substance has been conclusively shown to be as greatly affected by myocardial insufficiency. Since the pioneer investigation of Constabel, carried out on only a few hearts, it has become more and more apparent that this substance is decreased in the failing heart. On this point all investigators in the field are agreed. The underlying cause of the decrease in creatine content of the myocardium, however, has sometimes been challenged.

It has been suggested that the decrease in creatine is due to anatomical changes in the muscle, to hypertrophy of noncreatine containing parts of the cells, and to injury of the cell membranes, permitting the diffusion of creatine out of the cells.

Let us examine the evidence brought forward to show that the decrease in creatine is without significance. Determinations of the water content by various investigators have demonstrated that only a small fraction of the drop in creatine concentration can be assigned to this factor. While there is usually a small increase in the water content of the failing heart, and occasionally a significant increase, this factor is negligible with respect to creatine, although it may be of importance in itself as a factor interfering with the metabolic activity of the myocardium. The possibility that anatomical alterations, such as fatty infiltration and increases in connective tissue, may be responsible have been discounted by workers who have examined the heart histologically in conjunction with their analyses. At this point it is interesting to note that Hastings and his co-workers,²⁰ in experimental studies on the heart, have obtained quantitative evidence of chemical alterations in the absence of demonstrable histological changes. In our studies we have determined the water, fat and collagen content in a limited number of cases and have been unable to demonstrate any serious alterations in the values for creatine, phosphorus, and potassium after correction for these factors. Occasionally the fat and collagen content have been found to be increased particularly in the right ventricle, but these alterations in

individual cases exert a negligible effect upon the group of cases studied in this manner. It would, nevertheless, be highly desirable to have more extensive studies conducted which included the collagen content of the heart, especially in relation to age, hypertrophy, and infarction. Blumgart and his associates²¹ have recently measured myocardial fibrosis by chemically determining the collagen content and found that all cases having abnormally high collagen values, showed either marked coronary sclerosis with occlusions, or hypertrophy.

The possibility that injury of the cell membrane is responsible for the loss of creatine hardly seems credible. There is ample evidence in the literature to indicate that creatine may be taken up by muscle as well as released by it.

The final alternative then is that the loss of creatine is due to chemical events within the cell, an inability to maintain the creatine in the nondiffusible form of phosphocreatine. This loss in creatine is accompanied by, and apparently correlated with, losses in phosphorus, potassium and adenosinetriphosphate.

At the present time it would not appear that our knowledge of the chemistry of the heart can be readily applied to improve the treatment of myocardial insufficiency. Nevertheless, there is a definite relationship between the chemical events which occur in the heart and the therapy applied to congestive failure. The ability of the heart at any given time to contract will depend upon the summated result of all the factors that contribute this energy versus all those factors which tend to dissipate, consume, or interfere with the production. So far as we know at the present time, phosphocreatine and adenosinetriphosphate are the two substances most closely associated with the final stages in the transfer of chemical energy to mechanical energy. To build up this final reaction to its highest level, we are, therefore, interested in attaining two objectives: increasing the rate at which energy is made available and decreasing the demands upon the system. In other words, we are interested in maintaining the optimum concentration of phosphocreatine and adenosinetriphosphate and yet having them supply energy at an adequate rate, with the least possible dissipation. In the compensated heart the relative rates of the reactions centering about the phosphocreatine-adenosinetriphosphate system are such that energy input and energy expenditure are in equilibrium at a point where adequate amounts of phosphocreatine and adenosinetriphosphate are present.

At this point it is of interest to note that the chemical changes in phosphocreatine and adenosinetriphosphate, by which mechanical energy is released probably play a very important role in another connection, namely in the induction of the electric currents in the heart muscle which are recorded by the electrocardiograph. When the contractility and conductivity of the muscle cells are impaired, for example by infarction, with consequent loss of phosphocreatine and adenosinetriphosphate, characteristic electrocardiographic changes occur which can be related to certain areas of the heart.

Most of the established methods of treating heart failure are probably effective largely because they decrease the demands upon the heart, thus permitting the energy input to keep abreast of the expenditure. The most outstanding of these types of therapy are rest, digitalis, and the removal of edema through regulation of the water and electrolyte balance. The latter may exert some direct beneficial effect upon the myocardium by removing edema fluid from that tissue, thereby accelerating the metabolic transfer. The possible direct action of digitalis upon the heart muscle still remains a subject of controversy.

While it is generally believed that the fundamental causes of decompensation may be attributed to increased demands upon the heart to perform work and decreased ability to perform such work as a result of disturbances in the coronary circulation, these considerations should by no means limit the possibilities of bolstering the heart action by measures directly affecting the myocardium. Attempts have been made to increase the creatine content of the heart experimentally or to prevent its loss by the addition of creatine to perfusing fluids, but these measures thus far have met with little success. Similar attempts to increase the intracellular electrolytes of patients by feeding dipotassium phosphate have likewise met with failure. Kalter²² administered glycine, a creatine precursor, to patients with decompensated heart disease and reported several cases in which it apparently exerted a beneficial effect and was enthusiastic about the possibilities of this therapy. Herrmann and Decherd¹⁸ have also reported experiments in which the administration of glycine appeared to have beneficial effects. However, such studies are difficult to control, and one should be cautious in making interpretations.

Summary. We may conclude then that there is reasonably good evidence, direct and circumstantial, that phosphocreatine and adeno-

sinetriphosphate, as potassium salts, play an essential role in muscular activity, or more specifically are vital agents in the transfer of chemical to mechanical energy for muscular work. The chemical findings just reported on human heart muscle are in harmony with this hypothesis. Essentially normal values have been established for creatine, phosphorus, potassium and adenine in the muscle of the left and right ventricle. In the very early stages of cardiac hypertrophy there appears to be an increase in the concentration of these constituents, but with further hypertrophy all the values begin to fall and reach their lowest levels with extreme cardiac hypertrophy and heart failure. While it has not been definitely established that heart failure is due to the decreased concentration of these apparently vital constituents, or disproven that these changes merely accompany heart failure, the evidence appears to support the former view. Although the chemical observations reported have not as yet led to any established advance in therapy, still such data should materially aid in interpreting some of the clinical findings in diseases of the heart and in rationalizing treatment. It is hoped that the few observations reported may be the forerunners of more important biochemical studies on the heart.

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THE TREATMENT OF GOUT*

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INTRODUCTION

THE current trend in the management of patients afflicted with gout inclines toward acceptance of therapeutic principles that are physiologically sound or empirically satisfactory and rejection of those that fulfill neither criterion. Such a trend is encouraging in any malady and is particularly so in regard to gout because of the wide divergence of opinions which have been expressed in the past. There are several obstacles which have hindered progress in the evaluation of the treatment of gout and have delayed general acceptance of any regimen. In the first place, the etiology of gout is not known. The several theories are sufficiently dissimilar that treatment which may be directed toward correction of one causative mechanism may run counter to others which appear equally plausible to interested observers. Secondly, the pathogenesis of development of symptoms is inadequately understood. Evidence is not yet conclusive that gout is a disease primarily of articular or renal structures in contrast to a metabolic dyscrasia with joint and renal involvement as incidental processes. Thirdly, gout is a chronic disease and as in many chronic diseases there is great variation in the severity of somatic manifestations from patient to patient and considerable variation in the severity in afflicted persons during the natural course of the dyscrasia. Failure to appreciate this fact has led some physicians to attribute credit to a particular regimen, when in fact, the asymptomatic periods might have occurred irrespective of the treatment prescribed.

It is the conviction of the writer that there is no known cure for gout and that once the diagnosis is established the patient will have the malady throughout life. This does not mean that patients will have

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acute symptoms continuously if treatment be neglected. On the contrary, asymptomatic periods may persist for years in the absence of rigorous therapy. The malady, nevertheless, is a chronic disease as evidenced by (a) a persistent elevation of uric acid (urate) in blood and body fluids of all gouty patients, (b) failure of regression of bony changes once they have become visible by x-ray, and (c) progression of renal structural damage.

A liberal but not an inclusive interpretation of what is intended by the clinical term gout has been assumed in the preparation of this communication. Acute attacks of gouty arthritis, chronic deformed gouty joints, metabolic gout and gouty diathesis have been employed to express the various manifestations of the gouty dyscrasia. The first two phenomena are orthodox clinical realities and are recognized by most observers as such. Metabolic gout, i.e. a metabolic dysfunction responsible for the malady, persists throughout life in affected persons but the only suspicion of its presence between acute attacks of gouty arthritis is an increased concentration of serum urate and occasionally an increased excretion of urinary urate. The connotation, gouty diathesis, is mentioned frequently by various physicians although it is not universally accepted as a clinical entity. Several conditions, such as coronary sclerosis and gastrointestinal disturbances, have been attributed to the gouty diathesis in patients who show no evidence otherwise of suffering from acute gouty arthritis or metabolic gout. We are unwilling to subscribe to a catholic interpretation of the gouty diathesis and prefer to restrict its use in non-gouty persons to those members of gouty families who show an increased concentration of serum urate as discussed in the following paragraphs under heredity.

HEREDITY

It has been recognized for many years that the familial incidence of gout is high.¹ Recently it has been shown² that an increased concentration of serum urate in persons without gouty arthritis has a similar predominant familial incidence. Since 1935 more than 125 non-affected relatives of gouty patients have been investigated by us. The ages of the relatives varied from 6 to 86. Particular attention was given during the clinical questioning to the matter of joint symptoms in the past as well as to the clinical examination of joints for evidence of probable gouty arthritis. After a careful study it was concluded that none of the

supposedly non-affected members was suffering from gouty arthritis. The concentration of uric acid in the blood, however, was elevated in nearly 25 per cent of the total and was similar in magnitude to that observed in their kin who suffered from typical gout. In view of the early age at which some of the subjects were investigated, it seemed probable that the increased concentration of serum urate was present at birth or shortly after.

This phenomenon may be the true gouty diathesis. Of course it is also metabolic gout *sine* gouty arthritis. How many of the non-affected relatives will develop gouty arthritis subsequently will be most interesting. During the first six years after this study was started only one person with an elevated serum uric acid had an attack of gouty arthritis. It is possible that many will live a normal span of years without experiencing any attacks. Since gout manifests a strong male preponderance among afflicted persons, the tendency to gout is probably sex-linked and males rather than females should be watched for possible development of gouty arthritis. If the gouty diathesis is recognized in an otherwise healthy person, treatment should be similar to that recommended for intercritical gout with the exception that drugs are probably not indicated.

ACUTE GOUTY ARTHRITIS

The treatment of acute gouty arthritis should begin with the recognition of the prodromata of an impending attack. These include among other symptoms, polyuria, gastrointestinal unrest, suppression of sweating, and gain in body weight.³ Many of the prodromata accompany a fall in barometric pressure⁴ and at such a time the well informed patient will be particularly alert to the possibility of an impending attack. At the first appearance of premonitory symptoms, a few colchicine tablets (1/120 gr.) should be taken at hourly intervals. If the attack does not materialize within a few hours, further ingestion of colchicine is unnecessary. If symptoms progress from twinges and pangs to acute gouty pain, ingestion should be continued without interruption until an adequate amount of colchicine has been taken. The thought to be stressed at this point is the desirability of continual vigilance by the patient. It is probably no exaggeration to affirm that a few hours delay in beginning colchicine ingestion may determine the severity as well as the duration of acute episodes of gouty arthritis.⁵

A severe attack of gout may require from 8 to 16 colchicine tablets, the average is approximately 10, to achieve the desired effect. Adequacy is determined in the inexperienced by the appearance of untoward symptoms which include, nausea, diarrhea, and vomiting. Many patients learn from experience the optimum number of tablets to consume with each attack of acute gout and are able to obtain the desired alleviation of joint pain without the undesirable gastrointestinal symptoms. Until patients have acquired this information, it is imperative that the ingestion of colchicine be continued to the point of development of untoward symptoms before advising cessation. If a sufficient quantity of colchicine is taken, subsidence of joint pain usually begins after twelve hours and should be complete within a period of from twenty-four to forty-eight hours. A few acute attacks, less than 5 per cent in our experience, are not benefited materially by a single course of colchicine. If this be the case, a second course should be taken after a lapse of approximately three days. It is unwise to repeat the course earlier since gastrointestinal symptoms may develop before an amount of colchicine has been consumed adequate to affect joint symptoms.

General measures for the treatment of attacks of acute gouty arthritis include bed rest, an abundant fluid intake, a soft diet and sedatives. Bed rest usually is obligatory, nor is there any advantage to be gained by active motion of affected joints. A cradle for the bed clothes relieves local pressure upon involved structures. The application of hot or cold compresses contributes little since their soothing action is not great and alleviation of acute symptoms is not enhanced. An abundant intake of fluids is important and serves a dual purpose. During the acute stage of an attack there is an elevation of body temperature, increased sweating, and a decreased intake of water and salt from loss of appetite. Dehydration of the body may become pronounced and volume of urine output markedly reduced. With a restricted urine output there is an abnormally high concentration of urate in the renal tubules and precipitation of a portion of the urate as crystals. The damage to the kidney from this sequence of events may be one of the serious sequelae of an acute gouty attack. If the fluid intake is abundant, on the other hand, the internal environment of the body is maintained and volume of urine excreted is upheld. This can be achieved best by consumption of broths, soups, fruit juices and milk rather than by tea, coffee or sweetened beverages. The former fluids contain salts essential to the body which

are dissipated by sweating and need to be replaced in greater than normal amounts. A soft diet with a high percentage of carbohydrates is usually the choice of the sufferer. Aspirin, codeine, or morphine may be indicated to relieve pain. They usually are necessary for a period not exceeding twelve to twenty-four hours and should not be restricted if pain is severe.

INTERCRITICAL PERIODS

Acute attacks of gout should consume not more than a few days of each year; the great portion of the time then of any gouty patient is intercritical. Attention is centered as in the treatment of the acute attack upon physical activity, food, fluid and drugs. A gouty patient should be as active as possible between attacks. Prolonged bed rest after an acute attack has little beneficial effect upon gouty joints or upon the gouty dyscrasia and may be harmful in that it predisposes to an acute episode.

The diet recommended for gouty patients has been modified innumerable times through the centuries. The specific prohibitions have included carbohydrate, fat and protein. The conclusions of Ewart⁶ written in 1896 are illustrative: "In gout, more than elsewhere, because of its idiosyncrasies, we should beware of *dogmatism*. Gout is undoubtedly prevented by starvation; yet it does not follow that it may be cured on that plan. Gout may also be prevented by strict avoidance of animal food. This does not prove that it need in every case be treated on vegetarian principles. Again, although gout may fail to attack some of those whose diet is exclusively animal, we are not warranted in prescribing meat as the diet for gout. Each case should be studied on its own merits." In the first edition of *The Principles and Practice of Medicine*, Osler⁷ cautioned against the use of carbohydrate in gout as follows: "The conversion of azotized food is more complete with a minimum of carbohydrates than it is with an excess of them—in other words, one of the best means of avoiding the accumulation of lithic acid in the blood is to diminish the carbohydrates rather than the azotized foods. Meats of all kinds, except perhaps the coarser sorts, such as pork and veal and salted provisions, may be used. . . . Fats are easily digested and may be taken freely." The final statement is particularly interesting in view of the harm that has been attributed to fatty foods during the past decade.⁸ It has been argued that if an excessively high

fat diet, 200 gm. or more, were capable of inducing an attack of gout, a low fat diet, 25 gm. or less, would be beneficial. While most physicians agree that an excessively high fat intake is not desirable, restrictions are not usually placed on a diet with an average fat content.

Foods high in content of purines, such as liver, kidneys and sweetbreads should be avoided at all times. The consumption of a liberal portion of other meats is probably harmless in the absence of advanced renal insufficiency. If a patient relates a close association between the ingestion of an article of diet and an acute attack, the advisability of avoiding this food is self-evident. Most gouty patients, however, are unable to detect any close association and in the absence of suggestive data, a diet balanced in content of carbohydrate, fat and protein is advised. This sentiment was expressed more than 200 years ago by Cheyne" as follows: "And indeed Temperance, and Moderation in everyThing necessary for the Support of Life is best and safest."

A liberal intake of fluids is important in the treatment of interval gout as it is during an acute attack. Spas and watering places of previous generations made a real contribution because of the custom of insisting upon copious imbibation of mineral waters. The qualitative mineral constituents were probably less important than the quantity of fluid consumed daily. The mechanism of the beneficial action of a large fluid exchange is clarified by the recent advances in understanding of renal processes, particularly in regard to the exchange of water and electrolytes.

It has been shown recently that the amount of glomerular filtrate formed by a normal person is more than 100 cc. per minute. It is a very constant amount under controlled conditions and is not altered appreciably by variations in fluid intake. Since glomerular filtrate is a protein-free filtrate of plasma, the amount of electrolytes including urate, present in the 100 cc. of plasma, is excreted through the glomerular membrane per minute. Of this amount at least 98 per cent of water and sodium chloride is reabsorbed by the renal tubules. If fluid intake is small, the per cent reabsorbed is even greater and less than 1 per cent of water may be received by the collecting tubules and excreted into the bladder. The reabsorption of urate, on the other hand, is quantitatively unlike that for sodium chloride and always is much less. Instead of a 98 per cent reabsorption of salt, as mentioned above, only 90 per cent of urate is reabsorbed, leaving 10 per cent available for excretion into

the urinary bladder.¹⁰ If the solubility of urate were as great as the solubility of sodium chloride, the small amounts of water excreted would be sufficient to keep the large quantities of urate in solution. The solubility of urate in plasma and glomerular filtrate is near the maximum, however, and precipitation of urate and anatomical damage to the kidney are real possibilities. If a large amount of fluid is available for excretion because of a liberal fluid intake, precipitation of urate in renal tubules is inhibited.

The alcoholic content of fluids should be regulated by rules of temperance rather than abstinence. We have not observed any alcoholic beverage or group of beverages to be an offender in an appreciable number of gouty patients. A few patients sense the close association between drinking a particular beverage and onset of acute gouty arthritis. Avoidance of the particular beverage is recommended under such circumstances. Probably the most harm from consumption of alcohol is the quantity taken rather than the quality.

There are at least four types of drugs which have been used extensively in the treatment of gout. These are salicylates, cinchophen preparations, colchicine preparations and alkalis. Salicylates have a place in the modern scheme of gout therapy if it is believed desirable to "purge" periodically the body of urate. In 1879 Sée¹¹ discovered that salicylates increased the urinary excretion of uric acid. Two years later Campbell¹² wrote a treatise on their use in gout and pointed out that while salicylates increased the urinary output of urate, colchicum has no effect upon urate excretion. Salicylates have been used intermittently and sporadically since then for their diuretic action as well as for their analgesic action.

Cinchophen has an effect upon urate excretion^{13, 14} similar to that exerted by salicylate. There is no experimental data which suggests that either drug enhances urate output by altering the intermediary metabolism of purines.¹⁵ Neither is there any appreciable increase in amount of urate filtered by the glomerulus nor any change in permeability of the glomerular membrane for passage of urate. The site of action most likely is in the renal tubules¹⁶ and the process is one of inhibition of reabsorption of urate. The increased output in the urine is not unlike that which accompanies salyrgan diuresis¹⁰ and is produced by a mild toxic action on the tubules and impendence of normal reabsorptive processes. Since cinchophen is known to be toxic to the liver cells, it is pos-

sible that it is mildly toxic for renal tubular epithelium as well.

Cinchophen is not used regularly at the Massachusetts General Hospital because it is not believed to be indispensable in the treatment of gout. The incidence of cinchophen intoxication and death from acute liver poisoning throughout many parts of the world is noteworthy. Furthermore, the analgesic action in acute attacks is less reliable than colchicine. We are solidly behind the attempt of the Food and Drug Administration to reduce to a minimum the ingestion of cinchophen in this country. Neocinchophen is reputed to be less toxic than cinchophen. Its action on renal exchange of urate is less powerful and if a similar quantitative effect upon this mechanism is desired, proportionately larger amounts of neocinchophen are needed. The supposed advantage of neocinchophen over cinchophen seems questionable.

Colchicine is believed by us to be indispensable in the treatment of gout. Patients with gout should never allow themselves to be without a vial of colchicine, whether at home, at work or abroad. The use of hermodactyl, the botanical from which colchicum is derived, is credited to Alexander of Tralles who recommended it to gouty patients in the 6th Century A.D.¹⁷ In the 13th century Gilbert¹⁸ recognized the Alexandrian discovery and referred to the colchicum preparation in use at that time as "Cathopcie Alexanderine." Benjamin Franklin, a sufferer from gout, is supposed to have introduced colchicum into the United States following his sojourn in France.¹⁹ In 1820 Pelletier and Caventou²⁰ isolated the alkaloid colchicine from the meadow saffron or *Colchicum autumnale*. In the same year Haden²¹ discoursed at great length upon the merits of colchicum and mentioned, among other things, the benefit derived from its use in a case of inflammatory fever in a horse.

Colchicine, the active ingredient of colchicum and the substance to be preferred in the treatment of gout, has gained considerable fame in recent years because of its action upon mitosis in plants. To produce this effect it is necessary to give, per unit mass of experimental material, approximately 100 times the therapeutic dose recommended for gouty patients. Suffice it to say, we do not need to concern ourselves about inducing cancer by the oral use of colchicine in therapeutic amounts, since the gastrointestinal tract rebels if this limit is exceeded by even a few tablets.

The pharmacologic action of colchicine in gouty patients is not known. In 1854 Gairdner²² maintained that its beneficial action was not

related to an increased excretion of urinary urate. Recent studies in our laboratory have confirmed this.¹⁰ In acute gouty arthritis it is almost specific for alleviation of pain. It is ineffective in non-gouty types of acute arthritis. The action of colchicine in intercritical periods is less specific than during acute attacks but, nevertheless, is beneficial to most patients. The majority of those afflicted should take some colchicine from time to time.²³ Those who experience not more than one attack a year will need a few colchicine tablets (1/120 gr. each) only at times when mild aches and pains in the joints appear. All other patients should consume some colchicine regularly. This habit may vary from not more than one or two tablets a week to a daily ration of one or more. Patients who have several attacks of acute gouty arthritis each year before beginning treatment should take at least two tablets on each of three days a week. In a few instances of severe gouty arthritis, we have recommended two or three pills each day of the year. Several patients have followed this schedule for as long as five years and no untoward effects from the prolonged ingestion have been noted. Tolerance to the drug does not develop and if an acute attack supervenes, a full course of colchicine seems as effective as in patients who take the drug less frequently.

Alkaline waters and alkaline powders have some merit in the treatment of intercritical gout. The desirability of a large fluid exchange has been described. Alkaline powders have been advised because of the effect upon the hydrogen ion concentration of the urine. Urate is more soluble in an alkaline solution than in an acid media, the usual reaction of tubular urine. The increased excretion of urate in an alkaline urine, however, is quantitatively less than the increase which follows a large fluid exchange.

CHRONIC DEFORMING GOUTY ARTHRITIS

Low grade symptoms between attacks may persist in the joints of gouty patients with advanced structural changes. The symptoms are thought to be related to irreparable damage in the articular regions rather than to mild incipient acute attacks. Salicylates and colchicine are useful in control of such symptoms. Exercise is to be encouraged if the joints will permit it. Heat and massage are of little value.

The surgical treatment of chronically deformed gouty joints has not been explored extensively and until recently we have been reluctant to operate upon gouty joints. During the past five years, however, this

reluctance has been overcome chiefly because of the skilful management of the patients by R. R. Linton of the Surgical Service of the Massachusetts General Hospital. More than fifty operations have been performed upon gouty structures in more than twenty gouty patients during this interval. In some patients large tophi were removed from elbows, hands or feet. This was considered desirable because their size hindered normal movement of the limbs. In other patients, the urate tophi presented greater obstacles and the benefit was more pronounced by their removal. The patients were bedridden or semi-ambulatory from extensive deposition of urate in and about the articular structures of the feet. At least one tophus had broken down from trauma in each patient and a chronic sinus which discharged urate sludge persisted. Under such circumstances it was impossible to cleanse the sinus of bacteria before operation. In spite of almost certain contamination of the operative site extensive surgical procedures were consummated with no undesirable effects. Postoperative infection was never observed in any of the patients. None was treated before or after operation with any of the sulfonamide derivatives. The only specific drug given was colchicine. Three tablets were given daily for two or three days before the operation and for a similar period afterward. The incidence of postoperative acute gouty arthritis in patients prepared with colchicine was 8 per cent. In a control group of gouty patients not prepared with colchicine, the incidence of postoperative arthritis was 86 per cent. Of course the prophylactic use of colchicine at the time of any surgical procedure in a gouty patient is equally useful.

SUMMARY

The modern treatment of gout as practiced by the writer is outlined in this communication. It is thought to be easy to follow and temperate in its prohibitions. The judicious ingestion of colchicine (1/120 gr. tablet) during the premonitory, incipient and inflorescent stages of acute gouty arthritis convinces the most skeptical of its merit. During the intercritical periods some colchicine, depending upon the severity of joint involvement, should be taken. The incidence of acute attacks may be markedly reduced by this regimen but unfortunately progression of chronic deforming changes is merely delayed and not prevented. An abundant fluid exchange aids in the elimination of urate and inhibits deposition of urate crystals in the renal tubules. A diet balanced in re-

gard to minerals, vitamins and foodstuffs should be consumed. If the periodic ingestion of a substance which augments urate excretion is desired, salicylate rather than cinchophen should be chosen. There remains but one discovery to be made, i.e., some substance which will inhibit the increased formation of urate in the body. When this has become a fact, metabolic gout will be a medical curiosity and urate tophi unique.

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TROPICAL MEDICINE IN UNITED STATES MILITARY HISTORY*

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THE subject of this paper has been chosen not so much to paint a picture of the past as to indicate what diseases among those ordinarily included in the field of tropical medicine are likely to be encountered by our military forces in the present conflict, and how some of them may be controlled. The advance in medical knowledge has been so great since the settlement of this country and particularly since the Spanish-American war, that the present narrative will show the practical disappearance of certain diseases from our armed forces; but our adventures into the tropics in the task we have now undertaken may well fill us with forebodings as to many of these diseases, and we may find ourselves confronted with others which we have heretofore not encountered.

In order to indicate what has and what has not been accomplished in the control of tropical diseases in United States military forces up to the present time, I shall outline briefly the history of the more important ones.

THE DIARRHEAL DISEASES

The diarrheal diseases include bacillary and amebic dysentery, cholera, salmonella and staphylococcus food poisoning, and the non-specific diarrhea associated with the drinking of water polluted with sewage. Dysentery was one of the greatest handicaps to the permanent establishment of the Jamestown Colony which in essence was a military occupation. An epidemic of "bloody flux" assisted in the defeat of Braddock's campaign against the Indians in 1755. It undoubtedly was important in the War of Independence. During the War of 1812 it is said that on the frontiers in Vermont and New York State diarrhea and

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dysentery almost invariably overshadowed all other diseases and were the only ones which could be called camp diseases. The medical history of the War Between the States¹ devotes one of its two medical volumes entirely to the diarrheal diseases. The author of this volume, Joseph J. Woodward, was among the first to differentiate between the diphtheritic and ulcerative types of dysentery. He also recognized that it was often difficult to differentiate etiologically between dysentery and simple diarrhea. During that war there were recorded over 1,700,000 admissions for these diseases and over 44,000 deaths. They were the most important causes of illness in the Federal Army, and their case fatality rate increased progressively during the war, being six times as high in the last year as in the first. During the Spanish-American War the diarrheal diseases were reduced to about one-half their incidence in the War Between the States, but were second in rank only to malaria. During the World War they were under excellent control and had dropped to the seventh most important cause of illness. In France, however, there were several epidemics of bacillary dysentery in the A.E.F.,² and Emerson³ reported that immediately after the Chateau Thierry operation probably as many as 70 per cent of the troops engaged suffered from diarrheal diseases. In the Philippines, even during the World War, these diseases caused by far the highest admission and death rate among the American forces.

Although the pathological picture of amebic dysentery had been differentiated from that of bacillary dysentery by Councilman and Lafleur⁴ in 1891, and the pathogenicity of *E. histolytica* for man had been demonstrated in the Philippines by Walker and Sellards⁵ in 1913, the first World War gave the chief impetus to the modern study of amebiasis, which has brought out the high incidence of *E. histolytica* in the general population and the importance of drinking water and flies in its transmission. In the latter connection, Craig⁶ of the Army Medical Corps, described an epidemic of amebic dysentery among troops on the Mexican border in 1916, in which flies seem to have been the principal transmitting agent. We are still, however, not very far advanced in the control of amebiasis, since recent work indicates that the chlorination of water as prescribed for the killing of pathogenic bacteria will not kill the cysts of *E. histolytica*, although sand filtration, if properly conducted, appears to remove the cysts. This would probably be difficult in many situations in the present war. Craig's suggestion⁷ of the

use of Diodoquin in weekly doses as a prophylactic may be of value for troops whose water supply may be polluted.

The importance of salmonella and staphylococcus diarrhea has been recognized only in recent years. During the first World War an epidemic of diarrhea was reported in a unit of the A.E.F. which found it necessary to eat bread which had been insufficiently cooked. This epidemic may well have been caused by staphylococcus toxin. In the present conflict where troops may have to advance rapidly in the field or jungle far from safe water supplies, the temptation will be for them to slake their tropical thirst with polluted water, which may incapacitate them with diarrhea, if not with typhoid or dysentery. It is to be hoped that our individual soldiers will be furnished with chlorine tablets for use in their canteens as one safeguard against these diseases.

Effective vaccines against the dysenteries have not been developed, so that the protection of military forces against them in the present war must be conducted by the strictest possible sanitary measures.

CHOLERA

Cholera was first introduced into this continent in 1832 and proceeded at once to cause a catastrophe in our armed forces, and to use them as a source of spread to the civilian population. Troops of General Winfield Scott proceeding to the Black Hawk War from New York by way of the Great Lakes, lost two thirds of their command from cholera and desertion.⁸ Their progress was so delayed that they did not reach their destination until the war was over, but they did spread cholera down the Mississippi Valley. Again in 1867 cholera entered the United States and was spread by negro troops from Jefferson Barracks, Missouri, to other troops and civilians throughout Kansas and as far as New Mexico.⁹ These were apparently the only two pandemics of cholera in which our armed forces were involved, and fortunately the modern knowledge of the disease has kept it out of North America and Western Europe during this century. There was a general outbreak of it, however, in the Philippines as late as 1934 and it is still endemic in India and China. A serious epidemic occurred in the coastal regions of China in 1938. Cholera vaccine, although not strongly antigenic, confers a certain degree of protection for a few months and the disease will possibly be prevented in our armed forces during the present war by repeated vaccination of those who may be exposed.

TYPHOID FEVER

Typhoid fever was not clearly described until 1829 and was not clearly differentiated from typhus until 1837, so that earlier records of its incidence are unreliable. During the War Between the States¹⁰ over 75,000 cases and 27,000 deaths were ascribed to it. It stood next to diarrheal disease and malaria as a cause of illness and was second only to diarrheal disease as a cause of death. At that time Budd's demonstration¹¹ of the water transmission of typhoid fever had not been published, and although Woodward in discussing the etiology of the diarrheal diseases mentioned typhoid among the diseases which might be caused from "contagia" in the dejecta of the sick, he stated that the evidence was far from conclusive. The incidence of typhoid was highest in the first year of the war, the admission rate being 79 per thousand white troops. The rate decreased to 17 in the last year of the war but there was a steady increase in the case fatality rate from 25 per cent in the first year to 53 per cent in the last year. Whether this was due to exhaustion of the troops, to poorer care during more vigorous campaigns, or to inaccurate diagnosis is not indicated in the records. During the Spanish-American War typhoid fever was a major calamity. It took its chief toll among the volunteers, most of whom remained in the United States. Vaughan¹² gives the morbidity rate for typhoid as 193 cases per 1000, which means that nearly one-fifth of the troops contracted the disease. Deaths from typhoid constituted 86 per cent of the total deaths in the armed forces. The report of the investigating commission pointed out that the belief that typhoid was almost entirely transmitted by drinking water had led to the gross neglect of other sanitary methods of prevention. The lessons learned in this war, however, were invaluable for they indicated the necessity of rigid sanitation which thereafter became a major activity in the armed forces. Frederick Russell of the Army Medical Corps soon developed typhoid vaccine and in 1910 it was made compulsory for all personnel in the army.¹³ The typhoid admission rate dropped practically to zero in 1913, and has remained at a very low figure since that time. Even during the first World War it was of negligible importance, as only 1529 cases were reported. Most of these occurred in France during the offensives which carried the troops into areas rapidly evacuated by the Germans. The control of typhoid was one of the greatest accomplishments in military

medical history. It is to be hoped that in the present conflict this disease may be of minor importance. Colonel Joseph F. Siler and his collaborators at the Army Medical School have recently made an important contribution to our knowledge of immunity following typhoid vaccination by the development of the mouse-protection test, and have made it seem probable that a frequent small stimulating dose of vaccine following the initial three doses, will confer a reasonable degree of immunity to the disease. It should be emphasized, however, that in the first World War sanitation was probably more important than vaccination in preventing infection, since most of the cases occurred in vaccinated individuals and our troops were not exposed to the total lack of sanitation existing in most parts of the tropics.

MALARIA

Malaria probably always has been and still is the major endemic disease of most of the tropics inhabited by man. Recognized by the ancients, harassing the early settlers of this country, and taking its toll among civilians and soldiers alike until after the Spanish-American war, it has been deliberately controlled only in the most favored parts of the tropics and subtropics. During the War Between the States¹⁰ it was the second most important cause of illness in the Federal Army and the third most important cause of death. Including typho-malarial fever, most of which was probably estivo-autumnal malaria, its death rate was 26 per 1000 white troops. The annual case rate increased progressively during the war. These were northern troops operating mostly in the southern states and the increase in rate undoubtedly indicates a progressively increasing reservoir of infection, which spread the disease in the northern states after the war. In the Spanish-American war¹⁴ malaria was by far the most common disease. Its admission rate among volunteers, most of whom remained in this country, was 574 per thousand, and among Regular Army troops, many of whom went to Cuba and the Philippines, 695 per thousand. In other words, considerably over half of the troops had malaria.

In the occupation of Cuba following the Spanish-American War, Gorgas took measures not only against the yellow fever mosquito but against the *Anopheles* as well, and greatly reduced the death rate in Havana by drainage and other sanitary measures. When Gorgas transferred his activities to the Panama Canal Zone the malaria mortality was

reduced by similar measures but the disease has never been completely controlled because of the necessity of troop movements in unprotected areas.

We may expect a tremendous morbidity and mortality from malaria in the armed forces during the present conflict. Only by the most careful planning in advance can we hope to keep the incidence of the disease reasonably low, even in the predetermined bases established in the tropics. We have no true prophylactic against the disease. Quinine and atabrine when taken as prophylactic drugs merely postpone the development of symptoms in individuals bitten by infected mosquitoes. Already individuals connected with the defense program are returning from tropical areas suffering from the malignant estivo-autumnal disease. The relapse rate is high under the best known methods of treatment, and we may expect a large residue of chronic cases following the present war. Furthermore, the discovery that both quinine and atabrine decrease the efficiency of aviators at high altitudes, makes it inadvisable to use these drugs as preventives in these men, thus exposing the most important arm of the service to disability and ineffectiveness. There is indeed a great need for the discovery of a true prophylactic against malaria.

YELLOW FEVER

Yellow fever took its principal toll in this country before the War Between the States, although epidemics continued to occur as late as 1905. There is little evidence that it was important in our military history until the Spanish-American War. Then the campaign in Cuba and the subsequent occupation of the island made it an important military as well as civilian problem. There is no need to recount the brilliant work of the Army Research Board under Walter Reed in discovering the mosquito transmission of the disease, or Gorgas' successful campaign in eliminating it from Havana and the Canal Zone, or the practical elimination of it as an epidemic disease from Central and South America and the West Indies by the combined efforts of the Rockefeller Foundation and the Latin American countries. The brilliant work of the staff of the International Health Division of the Rockefeller Foundation in transmitting the disease to monkeys and mice, in determining its past and present distribution by the mouse-protection test and the viscerotome, in discovering its endemic existence in the

jungles of South America, and in developing an effective vaccine against it are also well known. Perhaps it is not so well known that the disease is endemic in Africa as far east as the Sudan, making the threat of its extension by rapid transport to the east coast of Africa and even to untouched Asia an ominous possibility. Although our armed forces will be protected by vaccination, they and commercial aviation may be the means of carrying it to virgin areas where *Aedes aegypti* can transmit it in its old epidemic form. No greater calamity to the people of Asia could result from the present war.

OTHER TROPICAL DISEASES

Certain other diseases of the tropics which have not in the past been important in our military forces, should be mentioned because of their possible importance in the present conflict.

Bubonic plague is endemic in China, Burma, Indo-China, Java, India, Africa, South America and the western United States. In the United States it is slowly moving eastward toward the Mississippi Valley. Epidemics of pneumonic plague are always a threat in North China and small epidemics have occurred recently in Ecuador. Although a vaccine is available for military personnel going into endemic areas, it gives only partial protection, and the destruction of cities may well cause the occurrence of epidemics to which troops may be exposed.

Typhus fever has not been an important disease in our military forces since the War of Independence but it devastated Europe during the first World War and has often been a determining factor in military campaigns. It is to be hoped that effective louse control will prevent its becoming important in the present conflict. The endemic murine type of the disease transmitted to man by the rat flea has extended considerably in the southern United States during the past twenty years and the possibility that it may be the source of louse-borne epidemics should be kept in mind.

Leprosy, although not very infectious, caused a few individual tragedies among our troops in the Philippines following the Spanish-American war and a few cases may be expected in veterans of the present war. Since the disease is endemic in Louisiana, Texas and Florida, the exhaustion of our people by a long war might contribute to its further spread.

Beri-beri need be mentioned only because of its prevalence among

the Asiatics with whom our forces will be associated during the present war. It should be recalled, however, that its high incidence in the Philippines led Vedder of the Army Medical Corps to make it the subject of important studies with regard to its treatment and prevention, and led R. R. Williams into the study which recently accomplished the synthesis of thiamine.

Dengue fever, the transmission of which by *Aedes aegypti* mosquitoes was conclusively demonstrated in the Philippines by Siler and his co-workers of the Army Medical Corps, has a wide distribution throughout the tropics and subtropics and periodically causes devastating epidemics even in the southern United States. It is possible that the disease may incapacitate large bodies of our military personnel in the Far East at critical times during the present war.

Trypanosomiasis is a distinct threat to troops operating in the interior of Africa, and leishmaniasis or kala-azar is widely prevalent in the Mediterranean area, India and North China. Schistosomiasis, the blood-fluke disease, acquired by contact with water containing the larval stage, is endemic in Puerto Rico and other West Indian islands, in the northeastern countries of South America, in Africa, the Near East, Central China, Japan, Formosa and the Philippines, and precautions must be taken to keep troops out of infected water if possible. Already a report has been received that American soldiers may have become infected in a shower bath supplied from an infected pool. Finally, mention should be made of the highly fatal Far Eastern rickettsial disease, Japanese river fever, which is transmitted by a mite and is present in Malaya.

The Golden Age of Tropical Medicine in United States history was the first two decades of the present century, when yellow fever, malaria, hookworm, typhoid and the dysenteries were largely brought under control. Representatives of our Army and Navy Medical Corps and the U. S. Public Health Service were very important factors in this work, and the Bureau of Science in Manila gave experience to many men who have become our leading authorities on tropical medicine. Most of the men responsible for this Golden Age have now died or retired from active service, and relatively few young men have entered the field to take their places. It is to be hoped that one benefit which may accrue from the present world tragedy will be the stimulation of another group of young men to undertake the solution of the

many problems in tropical medicine which still remain. It is deplorable that, as in the Spanish-American war, we find it again necessary to send most of our young medical officers into the tropics with little or no knowledge of tropical diseases. This war will probably be a long one and it is not too late for the medical schools of the country to make tropical medicine as important a subject in the curriculum as it will be for medical graduates who accompany our armed forces to the tropics.

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EFFECT OF TONSILLECTOMY ON RESPIRATORY INFECTIONS IN CHILDREN*

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RESPIRATORY infections in infants and in children comprise the most common group of illnesses for that age group. Statistical evidence points to a lowered mortality and morbidity rate from these diseases during the last ten years but no specific measures have been developed that assure reasonably certain control of these common infections. Though the common respiratory infections termed colds, sore throat or tonsillitis, laryngitis, bronchitis and pneumonia represent the usual manifestations in infants and in children, such complaints as otitis media, cervical adenitis and sinusitis must be considered as a part of or as sequelae of respiratory infections.

Before assigning to respiratory infections any causative or influencing factors certain data pertaining to these infections must be recognized. Though children at all ages may contract any of the respiratory infections it has been demonstrated that all of these infections are most prevalent in the age grouping of three to seven years. It is also certain that geographical location and climatic advantages influence the occurrence of these complaints. These accepted facts must not be lost sight of when any single factor is considered that might influence the incidence or course of these respiratory infections in children.

Definite progress has been made in the control of respiratory infections. Advances in the science of nutrition, particularly with reference to vitamin and mineral needs have played a part in developing resistance to respiratory infections. Epidemiological studies leading to a more intelligent handling of children have aided in this control. To immunological studies and recently to chemotherapy can be ascribed significant gains in the management of these common infections. For at least two decades there has been a strong conviction among the medical profession and in lay groups that the tonsils and the adenoids play a significant

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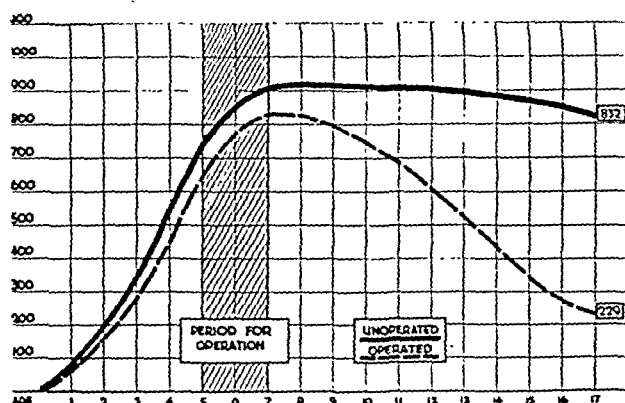


Chart 1. Tonsillitis and sore throat among 2,200 tonsillectomized and 2,200 nontonsillectomized children.

part in predisposing to or in prolonging these common infections in children. It is important therefore to study this supposed contributing factor to determine if possible the role of the tonsils and adenoids in respiratory infections.

Mindful of the fact that no scientific evidence is at hand to explain the part the tonsillar tissue plays in the economy of the child, it became necessary to follow the development of a group of children to adolescence, recording the sequence and the number of their respiratory infections over a period of years. It was possible to follow a group of 4,400 children for a period of ten years, half of whom had their tonsils and adenoids removed and the other half were not treated surgically. The initial examination and the observation of these children began when they were between the ages of four and seven years and continued into their high school period. At the time of their initial examination the indications for tonsillectomy were numerous but in general about the same for the entire group of children. For various reasons only one half of the total group (4,400) submitted to the operation, so the unoperated children served as controls. The incidence and the trend of a particular type of infection was noted in each child whether in the operated or in the unoperated group.

Tonsillitis: (Chart 1.) From these studies it was noted that tonsillitis was a common complaint in young children. Approximately 38 per cent of the 4,400 children utilized were subject to repeated attacks of tonsillitis (at least two febrile attacks a year) during the first seven years of life. As is indicated in Chart 1 the incidence of sore throat was de-

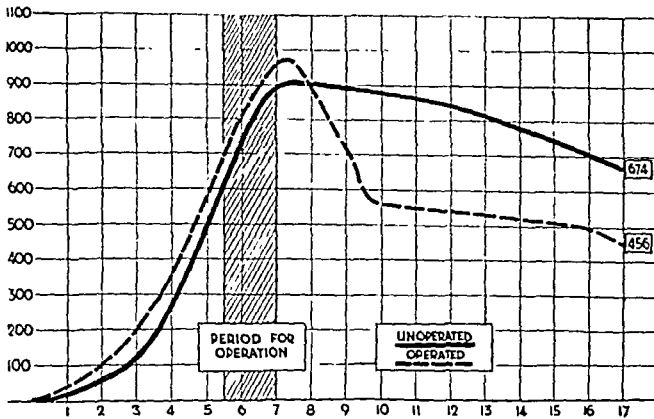


Chart 2. Colds (four or more a year) among 2,200 tonsillectomized and 2,200 non-tonsillectomized children.

cidedly lessened during the ten year period. In the group in which the operation was not done attacks of tonsillitis recurred with only a slight decrease in frequency during the same years. When one compares the incidence of this infection in the two groups it is obvious that the common ailment termed tonsillitis or sore throat occurred less frequently in the patients in whom the tonsils had been removed. In other studies, notably those of Selkirk and Mitchell,¹ similar results were obtained insofar as this complaint was concerned.

Common Cold: (Chart 2.) The common cold (four colds or more a year) occurred with about equal frequency in the two groups under observation. Approximately 42 per cent of the children were subject to this repeated infection up to the age of seven years. Over the ten year period the children who were operated on showed only a slight advantage over the children who were not, an advantage which cannot be considered statistically significant. It is quite likely that the removal of the adenoids benefited the younger children but as the children advanced in years the adenoid tissue retrograded, so that the children who were not operated on were likewise benefited. Though the trend, as far as frequent colds are concerned, is downward as the child increases in age, there is insufficient evidence to show that the role of the tonsils is a significant one, either in predisposing to or preventing this common infection. Adenoids, especially if they are obstructive, do play a significant part in predisposing to colds in young children but less so in older children.

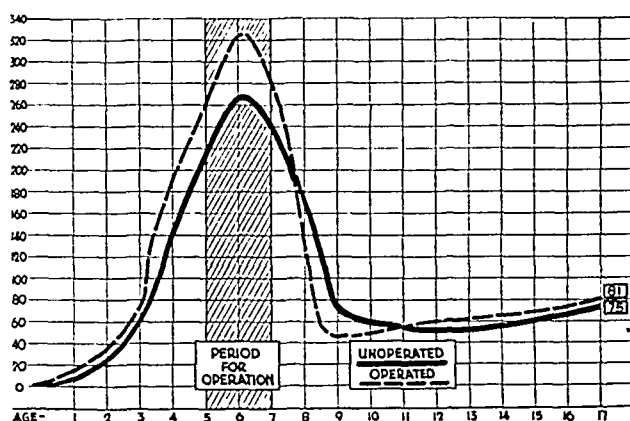


Chart 3. Otitis media (purulent) among 2,200 tonsillectomized and 2,200 nontonsillectomized children.

Otitis Media: (Chart 3.) Otitis media may exist independent of a respiratory infection but in many instances it occurs coincident with or as a sequela of other oral infections. Only purulent otitis media was considered in a study of this infection. It was noted that 15 per cent of the children who were subsequently operated on had suffered from purulent otitis media before the ages of from five to seven years, while in the control group 12 per cent were likewise affected. During the three year period following the tonsil and adenoid operation the incidence of otitis media was considerably lower in the operated group than in the unoperated children. It seems likely that the removal of the adenoids was responsible for this advantage, for during the next seven years the unoperated children fared as well and even a little better than those who were operated on. The age factor must be considered in evaluating the role of the tonsils and adenoids in this infection for, regardless of the presence or absence of the tonsils, this type of infection becomes less frequent after the eighth year of life. From these observations one can conclude that the tonsils play an insignificant role in the production of otitis media but that the adenoids may influence the incidence of this infection in children between three and eight years of age.

Cervical Adenitis: (Chart 4.) Cervical adenitis in children is usually secondary to a nasopharyngeal infection. It was noted that in each group, operated and control, 15 per cent of the children had definite enlargement of the cervical glands before the ages of five to seven years. Only

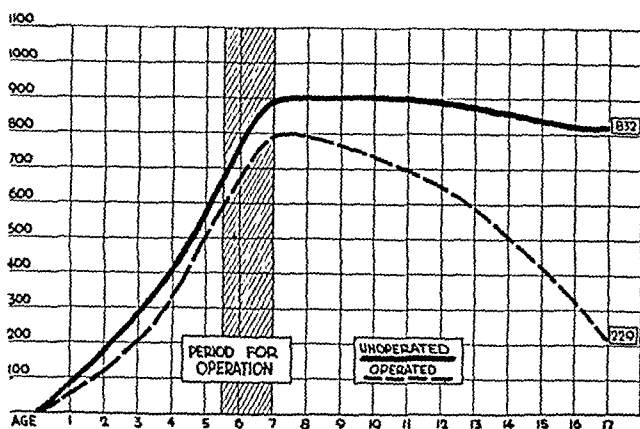


Chart 4. Cervical adenitis (acute and chronic) among 2,200 tonsillectomized and 2,200 nontonsillectomized children.

children in whom there was a visible enlargement of the cervical glands have been considered. During the three year period following tonsillectomy the incidence of cervical adenitis in the children who were operated on was 5 per cent as compared to an incidence of 14 per cent in the children who were not. Over a longer period of time a number of tonsillectomized children showed a recurrence of cervical adenitis, accounting for an incidence of 7 per cent at the end of ten years; while, among the children used as controls, the incidence of this complaint was 14 per cent. The statistical evidence in this study as well as in other reported studies shows a significant favorable trend for the relief of this complaint in the groups in which a tonsillectomy had been done.

Sinusitis and Nasal Allergy: Children with acute sinusitis, nasal allergy and allergic involvement of the sinuses are not favorably influenced by tonsillectomy. These conditions develop with equal frequency in children whose tonsils and adenoids have been removed in early childhood and in untreated children. The surgical removal of the tonsils and adenoids rarely benefits this condition. Observations made by Bullen² and recently by Hansel and Chang³ indicate that the role of the tonsils and adenoids is not an important one in the causation and treatment of these manifestations.

Laryngitis: Recurrent laryngitis occurred in 3 per cent of the children before the operation and in 5 per cent of the children in the control group over the same period of time. For the three year period following tonsillectomy the incidence was not changed in either group.

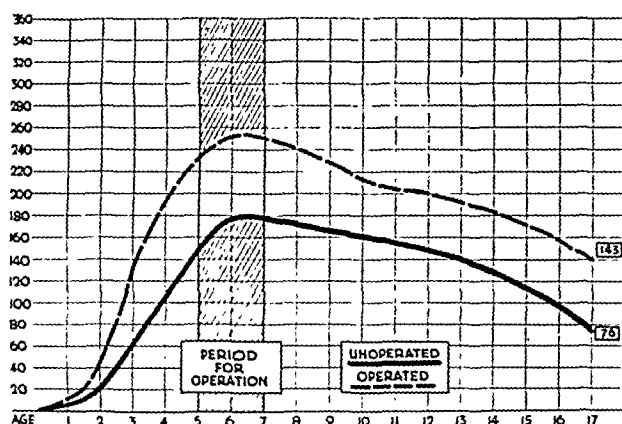


Chart 5. Pulmonary infections (bronchitis and pneumonia) among 2,200 tonsillectomized and 2,200 nontonsillectomized children.

At the end of the ten year follow-up period, 8 per cent of the children operated on were subject to recurrent attacks of laryngitis, while 10 per cent of the children used as controls were similarly affected. There is no obvious change in the incidence of this infection after the removal of the tonsils and adenoids and it would seem that the role of the tonsils and adenoids is not an important one in the occurrence of this infection.

Bronchitis and Pneumonia: (Chart 5.) In the case of upper respiratory infections the tonsils and adenoids are usually involved if they are present. In pulmonary infections these lymphoid structures may or may not be involved depending upon whether the pulmonary infection is primary or secondary to an upper respiratory infection. It is of interest, however, to discover, if possible, whether bronchitis and pneumonia occur less frequently or more frequently after the tonsils and adenoids have been removed. In analyzing the two groups it was found that pulmonary infections occurred more frequently in children during the first five years of life than in the next ten years. Such is the usual incidence of these infections. Undoubtedly some children subject to pulmonary infections are operated on because of this tendency, for more of the children who underwent the operation had repeated attacks of bronchitis and pneumonia before the ages of five and seven years than in the group of children who were never operated on. In spite of this, the trend was definitely for more pulmonary infections in the tonsillec-

tomized group over the ten year period than for the control children.

It seems that the absence of the tonsils either increased the chances of developing bronchitis and pneumonia or else the tonsillectomized group represented the more susceptible individuals and the operation was not responsible for the increased incidence of pulmonary infection. There seems to be no evidence to show that the tonsils and adenoids predispose the child to a pulmonary infection. There is suggestive evidence that the absence of the tonsils may encourage pulmonary involvement due to the fact that the soil in which bacteria might develop has been removed in the oral cavity.

When one reviews the statistical data dealing with the various infections it is quite evident that one can only talk about trends rather than what happens in an individual case. From clinical experience it is well known that the tonsils and adenoids play a very significant role in predisposing to respiratory infections, but can one deduce from these isolated results that the role of the tonsils is the same in all children? If it were so, the trends brought out by these statistical studies would be much more favorable for the operated group than our analysis shows. It can be assumed, however, that a favorable trend for a given infection in either group denotes the role the presence or the absence of the tonsils plays in the incidence of that infection. With that interpretation of the results it is clear that the tonsils and adenoids do play a significant role in the incidence of the upper respiratory infections while in the case of pulmonary infections the presence of the tonsils does not increase the incidence of bronchitis and pneumonia.

Recent advances in the treatment of respiratory infections may alter our opinion as to the significance of the tonsils and adenoids in these infections. The improved dietary factors which are now assured a large percentage of the children and the general use of sera and effective drugs in the treatment of respiratory infections have brought about a favorable effect on the morbidity and the mortality in these infections. The incidence and severity of respiratory infections has been shown to be less in adequately fed children than in children with known deficiencies in diet. The use of anti-pneumococcus serum and such drugs as sulfa-pyridine and sulfathiazole have materially reduced the mortality of pneumonia in children. Consequently the role of the tonsils and adenoids appears to be less important than during the period when no specific remedies were available. The control of the respiratory infections can-

not be considered accomplished however unless measures are developed that assure some degree of protection against the infection. It is in the field of prevention that the tonsils and adenoids may play an important role. One can therefore interpret the findings in this study as of significance in reducing the incidence of upper respiratory infections even though their removal does not tend toward a lower incidence of pulmonary infections.

DISCUSSION

After making due allowance for the various procedures that are known to influence the incidence and the treatment of respiratory infections in children, the evidence gathered from this study does indicate that there is a relationship between the tonsils and adenoids and respiratory infections. If one separates these manifestations into upper and lower respiratory infections it is clear that the tonsils and adenoids influence the upper type of respiratory infections and do not favorably influence the lower or pulmonary infections. It is probable that the presence of the tonsils may even act as a safeguard against pulmonary infection inasmuch as the unoperated children showed a slightly lower incidence of bronchitis and pneumonia. The measurable benefits of tonsillectomy and adenoidectomy to the children who have been subject to tonsillitis, colds, otitis media and cervical adenitis justify the operation in these children and make it a desirable procedure. The benefits however, though striking in the case of tonsillitis and cervical adenitis, are not great enough to advocate a prophylactic tonsillectomy in children with the idea of reducing the incidence of respiratory infections. The statistical evidence agrees with the general clinical experience that certain types of upper respiratory manifestations can be reduced if the tonsils and adenoids are removed but other manifestations may actually occur more frequently following the operation. The type of respiratory complaint to which the child is most susceptible must determine whether the tonsils or adenoids are likely to be a liability to the child. From clinical experience and from a study of the statistical evidence some idea is obtained as to the role of the tonsils and adenoids in the case of a specific complaint. Where the role of the tonsils and adenoids appears to be favorable to the production of clinical symptoms the surgical removal of the tonsils is advocated.

CONCLUSION

The tonsils are undoubtedly responsible for many upper respiratory infections especially in children subject to tonsillitis and to cervical adenitis and can be considered as playing an important role in these infections. Tonsillectomy is desirable in such children.

The adenoids appear to be a causative factor in some children who develop frequent colds and middle ear infections. In the age period of three to seven years the adenoid structures are particularly a menace to many children and their removal does assure some protection against similar recurrent attacks. Adenoidectomy is advised in such children either alone or along with a tonsillectomy.

For the relief and protection against sinusitis and nasal allergy no statistical evidence is available to justify any protection by either the removal of the tonsils or adenoids or both organs. In the production of these clinical manifestations the tonsils and adenoids seem not to play any significant part.

Evidence obtained in this study does not support the opinion that laryngitis, bronchitis and pneumonia can be reduced in incidence by removing the tonsils and adenoids. It appears that laryngeal, bronchial and pulmonary infections are not dependent upon the presence or absence of the tonsils and that these lymphoid structures do not play a significant role in lower respiratory diseases.

Improved hygienic and dietary measures along with successful specific therapy of pulmonary diseases have brought about a condition which justifies the statement that is now generally accepted that the role of the tonsils and adenoids in the average child is not as important today in the control of respiratory infections as was thought to be the case a decade or two ago.

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RELATIONSHIP OF UPPER RESPIRATORY INFECTIONS TO CHRONIC ARTHRITIS*

RALPH HENDERSON BOOTS AND ROBERT L. MCCOLLUM

DESPITE the fact that otolaryngology has reached a high peak in New York City, there seems to be as much chronic arthritis here as thirty years ago. Whereas there was one Arthritis Clinic in New York in 1920, now there are twenty-five, and all of them filled with patients. No one has gone so far as to place the blame for this on the Nose and Throat Surgeon, but these facts have been used as an argument against the removal of foci of infection for the treatment of the various forms of rheumatism.

Cecil and Angevine,¹ in a study of two hundred cases of typical rheumatoid arthritis reported that chronic focal infection played a comparatively unimportant role, and probably rightly stressed the idea that physicians should exercise a more conservative attitude regarding the treatment of tonsils, teeth, and sinuses. Recent writings such as this and discussions among rheumatologists have led to a swing of the pendulum away from removal of such foci. Perhaps it will swing too far and to prevent this, a review of our present knowledge is desirable, for we still believe that in certain cases of chronic rheumatism there is a relationship to upper respiratory infection. Surgical treatment is to be advised in many such cases, and one can expect definite improvement in the patients.

The thought that there could be a connection between dental or tonsillar infection and certain chronic diseases in the rest of the body goes back many years. However, it was not until the beginning of this century with the advance of bacteriology that this connection was popularized and an attempt made to place it on a scientific basis. Frank Billings,² in 1911, made the medical profession generally conscious of focal infection in the teeth, tonsils, sinuses, ears, gall bladder, appendix, urinary tract, prostate and bronchiectatic cavities. According to him,

* Read at the meeting of the Section of Otolaryngology of The New York Academy of Medicine, November 18, 1941.
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the chief systemic diseases which resulted from such infections were chronic arthritis, nephritis, cardiovascular degeneration, chronic neuritis and myositis. Many papers soon appeared in the literature on this subject and it was not long before a patient with chronic arthritis was examined primarily with the viewpoint of what further focus could be removed or treated. This period seems to have lasted until about 1930, when better methods of differential diagnosis of the various arthritic diseases lent a more critical attitude to such foci. No longer is the patient viewed as having "chronic arthritis," but as to whether or not he has rheumatoid arthritis (a chronic infectious form), osteoarthritis (a degenerative form), gonorrheal arthritis, tuberculous arthritis, gout or some other definite type. Obviously some of these were not primarily the result of "foci of infection."

During the past thirteen years of our investigations in the Arthritis Clinic at the Presbyterian Hospital, we have had an opportunity to make certain observations concerning this problem, and have gained definite impressions which can be presented. We see an average of one hundred arthritis patients each week, and it has been possible to make an accurate diagnosis of the type of arthritis in all except a very few cases. The ear, nose and throat examinations have been made by one of the authors, who has worked directly in the clinic in order to have a closer contact between the otolaryngologist and the internist. This direct collaboration has proven much more satisfactory than referring the patients for routine examination and care to the nose and throat clinic. In a preliminary report from our clinic in 1938, McCollom³ stressed the importance of an accurate diagnosis; that there are many types of arthritis that we are sure are not nose and throat problems. He had encountered three patients with gonorrheal arthritis in one year, who had had the tonsils removed in an attempt to clear up the arthritis, without waiting to establish the diagnosis of the arthritis involved.

It is necessary to discuss each type of arthritis separately in order to gain an understanding of any relationship. Certainly it should be emphasized that in each, statistical studies of improvement following removal of foci are of little value. One need only consider the difficulty of evaluating improvement in rheumatoid arthritis with vaccines, sulphur, gold, bee venom, etc. These are definite substances. How much more difficult it is to evaluate the effect of removal of so-called diseased tonsils, when frequently it is impossible to say whether or not they are

diseased! So, our conclusions are drawn not so much from statistical studies as from a better understanding of the disease processes of the type of arthritis considered.

RHEUMATOID ARTHRITIS

(Synonyms: ATROPHIC, CHRONIC INFECTIOUS ARTHRITIS)

About two-thirds of all cases of chronic arthritis fall fairly equally into one of two groups—rheumatoid arthritis and osteoarthritis.

The first of these, rheumatoid arthritis, is thought to be an infectious disease, in contradistinction to osteoarthritis which is considered a degeneration or “old age” of joints. It rarely kills, so that we see these fairly young patients year after year, and every form of therapy is tried. They are subjected to all sorts of cures. This has been the type of arthritis above all others in which it has been considered justifiable to remove any focus of infection, especially dead teeth or tonsils.

The typical picture is that of a young adult, thin, with symmetrical spindle-shaped or fusiform swelling of joints. The patient frequently has low-grade fever, anemia, vasomotor changes, subcutaneous nodules and sometimes enlargement of liver and spleen. It is a systemic disease and not one simply of local involvement of the joints. It occurs three times as frequently in women as in men. It is a disease of temperate climate—the farther south one goes, the less the incidence of the disease, it being practically unknown in tropical or desert regions. The incidence corresponds closely to that of hemolytic streptococcal diseases. Sixty per cent of such cases have agglutinins for hemolytic streptococci in their blood sera and this finding is used for differential diagnosis—such agglutinins not being found in any other chronic disease. Most investigators have held that there may be a definite relationship between this disease and hemolytic streptococcal infection. This relationship, however, is not definite, as no bacteria can be recovered from the blood stream or the joints of these patients. Instances in which the disease is ushered in by infections of the upper respiratory tract occur so frequently that a causal relationship is suggested. In some there appears to be a definite association between an attack of tonsillitis and the onset of the disease, while in other cases the sinuses seem to be responsible.

In Tables I and II is an analysis of 180 cases of rheumatoid arthritis, with reference to upper respiratory infections. Table III shows the results of tonsillectomy in this group.

TABLE I

RELATIONSHIP BETWEEN UPPER RESPIRATORY INFECTIONS AND RHEUMATOID ARTHRITIS IN 180 CASES

| <i>Group</i> | | <i>Cases</i> | <i>Percentage</i> |
|--------------|--|--------------|-------------------|
| A | History of Upper Respiratory Infections (frequent sore throats, colds, grippe or sinusitis; much more frequent than average) | 92 | 51% |
| B | Average or Less Than Average Upper Respiratory Infections | 88 | 49% |

TABLE II

92 CASES OF RHEUMATOID ARTHRITIS WITH FREQUENT UPPER RESPIRATORY INFECTIONS (Group A, Table I)

| | <i>Cases</i> |
|---|--------------|
| Rheumatoid Arthritis Cases—Onset Immediately Following Upper Respiratory Infections | 37 |
| Rheumatoid Arthritis Cases Accompanied by Sinus Infections | 58 |
| (a) Purulent Sinusitis* | 30 |
| (b) Non-Purulent Sinusitis | 28 |

* In most cases with the treatment of the purulent sinusitis, there occurred an improvement of the rheumatoid arthritis.

TABLE III

RELATIONSHIP BETWEEN TONSILS AND RHEUMATOID ARTHRITIS IN 180 CASES

| | <i>Cases</i> | <i>Percentage</i> |
|--|--------------|-------------------|
| Apparently Improved by Tonsillectomy (Practically all of these belong to Group A, Table I) | 25 | 14% |
| Not Improved by Tonsillectomy | 47 | 26% |
| Tonsils Removed Before Onset of Rheumatoid Arthritis | 38 | 21% |
| Tonsillectomy Not Advised | 54 | 30% |
| Tonsillectomy Advised but Pending | 16 | 9% |

From these figures and our clinical impressions, we have concluded that: (1) In 20 per cent of the cases examined, the disease seemed to be ushered in by an upper respiratory infection. (2) Patients with rheumatoid arthritis accompanied by purulent sinusitis usually improved with adequate treatment of the sinus infection. Such purulent sinus infections were found in 17 per cent of our cases. (3) It also seemed to us that the rheumatoid arthritis increased greatly in activity with any intervening upper respiratory infection. (4) The relationship between upper respiratory infections and rheumatoid arthritis has not been shown to be specific, and any improvement which occurs following the removal of tonsils and treating of purulent sinuses may be indirect, as it has long been known that anything which improves the general health helps this disease. (5) In years past, the importance of nose and throat infections in this disease has been overemphasized, but the internist who entirely ignores the presence of such infections seems to us guilty of neglect. (6) Although it seemed that measurable improvement frequently followed removal of diseased tonsils, yet routine tonsillectomy would not seem to be indicated, as it did not cause improvement in any convincing number of cases.

OSTEOARTHRITIS

Osteoarthritis, or hypertrophic arthritis, the other common form of chronic arthritis, is probably a degenerative disease—beginning at the time of life when other degenerations occur, and is probably as much a part of old age as the graying of the hair. The patient is past forty years, male and female equally involved—usually no history of following an upper respiratory infection. The patient is usually well-nourished or obese and healthy-looking. The joints involved, except for the distal joints of the fingers, are the weight-bearing joints—hips, knees, and spine. These patients are greatly benefited by rest, weight reduction, physical therapy and spa therapy. Exposure to cold frequently aggravates their complaints, just as occurs with old fracture cases, and with these old people, it is frequently desirable to have them spend their winters in a warm climate.

Focal infection rarely plays any demonstrable role, and one should not expect any improvement in the symptoms from tonsillectomy or treatment of sinuses. The indications for such treatment in patients with osteoarthritis should be on other grounds than their arthritis.

RHEUMATIC FEVER

Very few cases of the acute type of rheumatic fever come to an arthritis clinic. A moderate number of cases with sub-acute or chronic involvement of the joints are seen with or without cardiac damage. Like rheumatoid arthritis, rheumatic fever is a disease mainly of temperate climates and apparently associated with hemolytic streptococcal infection. Most attacks begin in the early spring, the season of most frequent respiratory infections. In over 50 per cent of the cases the attack is preceded by acute sore throat, tonsillitis or sinusitis. The acceptance of the hemolytic streptococcus as the direct etiological agent is not general, many observers holding that the prodromal hemolytic streptococcal infection of the throat merely permits entrance of the true causative agent, or in some other way activates the disease.

In regard to treatment of upper respiratory infections in these cases, we take the liberty of quoting Swift,⁴ who has had much more opportunity to form an opinion: "Rheumatic fever follows tonsillitis so frequently that tonsillectomy seems indicated if these organs remain diseased; for they may be the site of production of sensitizing substances or areas of infection whence bacteria are discharged into the blood stream. Preceding operation on any focus of infection, tonsils, sinuses or teeth, the patient should be placed under the influence of antirheumatic drugs in an attempt to prevent possible relapses. But the removal of tonsils does not insure absence of recurrences of the disease, for patients may have other sources of sensitization or may incur reinfection with hemolytic streptococci.

"Finally, in our present state of knowledge, it appears that the best prophylactic measure is to keep the patient free from hemolytic streptococcal infection. This indication is more easily stated than consummated. But public health measures of the future must recognize this important factor in the prophylaxis of infectious heart disease."

We have been especially interested in a group which seems to be a chronic form of rheumatic fever and includes many cases of that type of rheumatoid arthritis known as secondary progressive polyarthritis. These were formerly considered as rheumatoid arthritis following rheumatic fever, but the more we have studied them, the more it has seemed possible they are merely cases of chronic rheumatic fever. Clinically, the joints have the typical appearance of rheumatoid arthritis,

i.e., symmetrical fusiform swellings. However, the blood sera of these cases do not agglutinate hemolytic streptococci and they uniformly exhibit a high antistreptolysin titer. We have looked upon these cases as adult rheumatic fever. Practically all of them give a history of frequent sore throats or sinus infections, and experience indicates that it is very important in this group to remove diseased tonsils and treat sinusitis.

INFECTIVE ARTHRITIS

Tuberculosis of joints, gonorrheal arthritis, arthritis occurring with lymphogranuloma venereum, lues, typhoid fever, suppurative arthritis due to staphylococci and hemolytic streptococci obviously have no relation to upper respiratory infections. Arthritis due to meningococci may have its origin in an upper respiratory infection with that organism.

GOUT

Most physicians usually think of the acute attack of gouty arthritis as following dietary or alcoholic indiscretion. This conception is only part of the picture. Acute gout is precipitated just as frequently in the gouty individual by any acute infection. It is often surprising to see a gouty patient develop an acute attack during the convalescence from pneumonia, after having been for days on a soft or liquid diet and no alcohol.

We personally have seen a number of acute attacks of gout precipitated by antrum infections and acute tonsillitis, and it would seem logical to treat these.

FIBROSITIS

Other than rheumatoid and osteoarthritis, fibrositis is one of the most common conditions encountered in our clinic, and it is probably much more frequently seen in private practice. It is an umbrellalike term, not clearly defined, which includes bursitis, myositis, neuritis, and most non-suppurative inflammations of the supportive fibrous tissues. Certainly at the present time the term "fibrositis" is too loosely used and too frequently applied to any unexplained skeletal pain. Some authors divide fibrositis as follows: (1) Primary fibrositis, with involvement of fibrous tissue independent and not a part of any other disease; (2) secondary fibrositis; fibrous tissue changes secondary to rheumatoid arthritis, specific infections, trauma, etc.

In this presentation, we are concerned only with primary fibrositis. Many cases of morning stiffness of muscles, torticollis, lumbago, painful shoulders, are included as fibrositis. The etiology and pathology of most of these has not been determined and there is a definite need for investigation to clarify this problem.

Many of these cases seem to be related to upper respiratory infections, although the relationship has been difficult to prove. Most physicians have encountered painful shoulders, torticollis, and muscle aching accompanying sore throats, sinus infections, and recurrent colds. Usually with this group, improvement of the fibrositis may be expected with successful treatment of the sinusitis or removal of the diseased tonsils.

FOCAL INFECTION ARTHRITIS

Modern classifications of arthritis do not recognize this term, and it is presumed by us that such cases should be classified as "infective arthritis, etiology unknown." Whatever name is given to these, we definitely see a very small group of cases which might truly be called focal infection arthritis. These are usually monarticular, and when they occur, the removal of the focus causes a disappearance of the arthritis. A most striking example of this, although not related to upper respiratory infection, was a young patient whom we had observed for a long period for recurring hydrarthrosis of the knee. Each time this knee flared up, she exhibited tenderness over the appendix. After removal of the appendix, the knee became entirely well. The mechanism of these cases is not known. Such cases also occur related to purulent sinuses and tonsillitis, and the results of the removal of the foci are most striking. These true focal infection arthritis cases are *rare*.

CONCLUSIONS

1. *Routine* tonsillectomy is not indicated in any form of arthritis.
2. A diagnosis of the type of arthritis should be made, before considering any relationship to a respiratory or any other focus.
3. Certain types of arthritis, such as osteoarthritis, gonorrheal arthritis, tuberculous arthritis, etc., are definitely *not* related to upper respiratory infection.
4. In rheumatoid arthritis particularly, it is wise to remove tonsils which seem diseased and to treat sinus infections, not because of any

proven etiological relationship, but because anything which improves the health of these patients seems to help their arthritis.

5. The question of tonsillectomy or treatment of sinusitis in any given case still is largely one of clinical judgment of the physician. Decision regarding such treatment is better made by combined study by the internist and otolaryngologist.

6. The necessity of taking a very careful history of upper respiratory infections in these cases is stressed.

7. Early treatment of the sinuses and early removal of the tonsils is necessary, if one is to expect any benefit in the rheumatoid arthritis group.

8. The results in private practice are probably better than in the clinics, as they are usually seen earlier and possible foci are treated and eradicated at an earlier stage of the disease.

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TONSILLECTOMY AND ACUTE NEPHRITIS*

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HERE is no doubt about the close relationship between streptococcus infection (chiefly of the upper respiratory tract) and the pathogenesis of acute nephritis. Clinical, bacteriological and immunological studies give evidence of *Streptococcus hemolyticus* invasion in over 90 per cent of the cases of acute glomerulonephritis. The *Streptococcus hemolyticus* may come in through any portal but in the great majority of cases it comes in through the upper respiratory tract and associated structures. For our purposes there is not much use in making accurate anatomical diagnoses, since all the structures involved are not only contiguous but continuous.

In contrast to rheumatic fever the type of infection in nephritis is quite different. Instead of a mild, evanescent sore throat, such as precedes the rheumatic attack, the child who gets nephritis has a deep infection, such as cervical adenitis, mastoiditis or peritonsillar abscess. It is not the uncomplicated case of scarlet fever or tonsillitis that develops nephritis. What brings many children with nephritis to the clinic or hospital is not the nephritis but the cervical adenitis or mastoiditis, and the nephritis is discovered on routine examination. Having established a relationship between hemolytic streptococcus invasion of the upper respiratory tract and nephritis the question arises as to what can be done about it and, in particular, what is the effect of tonsillectomy.

Prophylaxis: There is no evidence that tonsillectomy plays any important role in preventing acute nephritis. Illingworth in England reported that 20 per cent of a large series had had tonsillectomy some time before the onset of acute nephritis. In Boston, Wessellhoeft reported the same incidence of postscarlatinal nephritis in those children with and without tonsils. In our series at the Babies Hospital approximately one-third of the patients with acute glomerulonephritis have had their tonsils removed. I do not see why one could expect a prophy-

* Read November 19, 1941 before the Section of Otolaryngology.

lactic effect, since the children who are destined to have acute nephritis are subject to repeated attacks of upper respiratory infection, and tonsillectomy in this group of children does not seem to materially lessen the incidence of upper respiratory infection. A point in the prophylaxis of nephritis which may be brought out here is the management of the preceding infection. If this primary infection could be treated so as to prevent the recrudescence of infection in the second to third week, which may be a precipitating factor in nephritis, it is conceivable that some cases of nephritis might be prevented. Obviously tonsillectomy and adenoidectomy do not prevent the septic complications which accompany acute glomerulonephritis. All forms of treatment in scarlet fever are said to lessen complications. None of the data is convincing. Chemotherapy offers an opportunity for a carefully controlled study of this question.

Shall tonsils be removed in cases of acute glomerulonephritis? When shall the operation be done? What are the results? Presumably the object in tonsillectomy in these cases is to prevent the development of chronic nephritis by removing a focus of infection which may be causing persistent renal damage and lessening the incidence of upper respiratory infection which also may further damage the kidney. There is no basis in fact for this conclusion. If we knew which children would develop chronic nephritis, the question could be answered. It is quite true that in the majority of children the improvement and healing process in nephritis parallels closely the activity of the infectious process and that, with persistence or recurrence of infection, urinary changes of a definite degree persist and recur. But I have seen prompt healing of the nephritis in the presence of persistent infection and I have seen nephritis progress into the subacute and chronic stage without any clinical evidence of infection. All of the above things can happen regardless of the presence or absence of tonsils, or tonsillectomy in the acute stage.

When chronic nephritis has become established I have never been convinced that any attack on foci of infection has altered the established course of the disease. Our experience is in agreement with that in Baltimore—that tonsillectomy did not prevent infection or exacerbation of the nephritis and that other factors must operate for recovery or progression. "The end is determined by the beginning."

With these divergent opinions and without any rational basis for action, what then is a reasonable attitude for the clinician to take. He

has to meet this problem and make a decision. Even though we are ignorant of the etiology and pathogenesis of glomerulonephritis, there does appear to be a relationship in some individuals between upper respiratory infection and nephritis, and if any of the generally accepted indications for tonsillectomy are present in a case of either acute or chronic nephritis, perform the operation. Nephritis itself is not to be considered an indication for tonsillectomy and adenoidectomy. It is an elective operation and the time for operation had best be decided for each individual case, preferably when the symptoms and signs of the nephritis have subsided and the pharynx is not acutely inflamed. When this is done, severe reactions have not been encountered in my experience, but I must admit that the beneficial effects are not proven.



GALILEO *

ARTURO CASTIGLIONI

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GALILEO GALILEI was born at Pisa on February 15, 1564 when the Italian Renaissance was at its greatest height. His father Vincenzo, was an able mathematician, and a skilful musician. Galileo was educated at the monastery of Vallombrosa, near Florence, where he studied Greek, Latin and logic. In 1581 he went to the University of Pisa to study medicine. He devoted several years to these studies, and then yielded to his greater interest in mathematics and physics.

* In commemoration of the three-hundredth anniversary of the death of Galileo held at The New York Academy of Medicine.

While watching a lamp swinging in the cathedral he observed that whatever the range of its excursions they were invariably equal in time. The experimental verification of this fact led him to the discovery of the isochronism of the pendulum. Galileo immediately applied the new principle to the timing of the human pulse.

In 1585 Galileo returned to Florence, and in 1586 published the first description of his invention of the hydrostatic balance. His name soon became known throughout Italy. From 1589 to 1591 he carried on a series of experiments to determine the first principles of dynamics. His demonstration made from the Leaning Tower, before the professors, the students, and the people of Pisa, that bodies of different weights fall with the same velocity, marks an epochal achievement in the history of experimental science. In 1592 he was called to the University of Padua where he held the chair of mathematics until 1610. There he attracted the attention of students and persons of distinction who came from every part of the world.

The men of the Renaissance had set out to explore the nature of man and the cosmos. Man then was disclosed through the study of anatomy, pathology, physiology, and biology. Vesalius had already revolutionized the study of anatomy; Paré had modernized surgery. The studies of Cesalpino and Fabrizio had solved many important physiological problems, and Fracastoro had launched the new doctrine of the infectious nature of certain diseases. At this time too the discovery of countries, of plants, of animals, and of human species, until then unknown, further extended the intellectual horizons of the Age. The universe appeared then infinitely larger and more vast than the human mind had been able to conceive it. The relationships of man with all living things, with the sky and the earth, with animals and plants, appeared very different from those which had been accepted until then, and which had placed man in the center of the universe. Nevertheless, the belief that the earth was the center of the cosmic system seemed, because of its dogmatic character, to be unassailable and impregnable. Copernicus' discovery, though wonderful in its grandeur, had upset neither the supporters of the Ptolemaic doctrine nor those who believed every contrary statement to be inadmissible and heretical. The Copernican doctrine, expounded in a book written in rather obscure terms, and aiming primarily at the reform of the calendar, had not yet roused the protests of the strict supporters of the dogmas. Galileo, who had

begun by destroying with experimental proofs the principle of Aristotelian mechanics, had collected all the facts justifying complete acceptance of the Copernican theory, and had sensed the importance of Kepler's demonstration in 1609 that planetary orbits are elliptical. This discovery ended the Aristotelian dogma, which held that no celestial movement was possible except in a circular pattern.

Galileo succeeded in 1609 in producing a telescope of three-fold magnifying power; later he improved it until it had a magnifying power of 32. His instruments, of which he manufactured hundreds, were soon in demand in every part of Europe. His astronomical observations made with the aid of his telescopes so perfectly substantiated the truth of the Copernican doctrine that in 1610 he publicly proclaimed his convictions in the book, *Sidereus Nuncius*.

Galileo's discovery of the phases of Venus and of the satellites of Jupiter gave added proof to his belief. To save the crumbling edifice of dogmatism, however, the Tribunal of the Holy Inquisition declared the doctrine that the sun and not the earth is the center of the universe, and that the earth moves in its own orbit, to be absurd and heretical.

In 1632, at the time when the scientific world was upser by Harvey's discovery and experimental proof of the circulation of the blood, Galileo published in Italian, that is in a language accessible to the common people, his *Dialogo dei due Massimi Sistemi del Mondo*. This was greeted with tumultuous applause in every part of Europe. The strength and clearness of scientific exposition were here happily combined with great elegance of style. But this remarkable book was in flagrant violation of the decree of the Holy Office, and the author was cited to Rome by the Inquisition. On June 22nd the Tribunal compelled the 70-year-old man to recant, sentencing him to incarceration at the pleasure of the Tribunal, and enjoining him by way of penance to recite once a week for three years the seven penitential psalms. The judges doubtless had the illusion that they had defeated every attempt at rebellion, and had saved dogma by means of a punitive decree.

In reality however, Galileo's demonstrations effected a great revolution in thought to which the discovery of the microscope gave added impetus. In 1610 Galileo had adapted telescope lenses to the magnification of extremely small objects and constructed an instrument for the examination of the organs of very small animals. In 1614 he spoke about it to several friends, and D  tarde, a scientist who visited him at

Florence, stated that with the aid of this instrument he had seen flies that were as big as sheep, and had observed that they are covered with hair and provided with angular joints. To this instrument a Greek scientist, Demisciamo, member of the Accademia dei Lincei to which Galileo belonged, gave the name "microscope." About the same time Galileo constructed the first thermometer, an air-thermoscope consisting of a glass bulb containing air connected to a glass tube or small ball dipping into a colored liquid. These successes of Galileo were in large measure due to his skill in perfecting the instruments he employed. He was thus the inventor of an effective telescope and of the compound microscope.

Galileo's conception of a mechanical universe dominated by mathematical laws swiftly reacted on the biological sciences. His conception of the cosmos proved that mechanical principles rule alike in the movements of the heavens and in the changes on the earth, in the revolution of a planet's satellites and in the structures of the human body.

Galileo's work was, therefore, not only creative in the field of astronomy but affected all scientific thought from its foundation. Scientific thought turned definitely toward experimental research following his principle: "the right way to attain truth is to put experience before all discussions." Attacking dogmatism with the greatest courage, he affirmed: "it is foolish to seek the meaning of natural things in the writings of this or that author, rather than in the works of nature which are always alive and at work before our eyes, true and unchanging in all their manifestations."

Galileo spent the last years of his life in his villa at Arcetri, in the strict seclusion which was the prescribed condition of his comparative freedom. His mental activities, however, continued undiminished till the last day of his life. He published in 1636 his *Dialoghi delle Nuove Scienze* in which he summarized the results of his experiments. His last discovery—of the moon's diurnal and monthly digressions—was made in 1637. Then he became blind. His genius, however, was at work until the last moment. As a teacher, as a philosopher, as a thinker, he was still active when he died on January 8th, 1642.

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BULLETIN OF THE NEW YORK
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BULLETIN OF
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JUNE, 1942

NEUROCIRCULATORY ASTHENIA
AND RELATED PROBLEMS IN
MILITARY MEDICINE *

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INTRODUCTION

WITH the advent of the second World War the problems of neurocirculatory asthenia have returned in Europe, and have been revived in this country in connection with the examination of draftees and volunteers. It is a disorder of individual and social importance even in peace time; but with war or the threat of war, it becomes imperative for the Army and Navy to avoid cluttering up their combat services with men who may break down with neurocirculatory asthenia, become incapacitated, and finally through pensions and invalidism become a permanent financial burden to the country. These are practical reasons for again considering the subject, but in addition our concept of the condition has undergone modification since 1917 when Thomas Lewis^{1,2} and others brought out the admirable reports of their experience with the effort syndrome in the British Army. Something more is now known of the etiology, pathologic physiology, symptomatology, signs,

* Read October 15, 1941 at the Graduate Fortnight of The New York Academy of Medicine.

diagnosis, prognosis, and possibly even of treatment than was known in 1917. These are the important reasons for reconsidering the whole subject at the present time.

Definition: Neurocirculatory asthenia is a clinical syndrome, not a disease sui generis, characterized by dyspnea, palpitation, chest pain, exhaustibility, dizziness, headache, nervousness, and a great variety of associated symptoms and signs called forth or increased by effort, and in which no evidence of structural disease can be found to which the symptoms may be related.

Terminology: A dozen other names have been used at various times by different authors. Out of deference to Da Costa one would be tempted to use the term he originally introduced, "The Irritable Heart," but there are great practical objections to the use of any name which directs attention to the heart. Very recently in his admirable lectures Dr. Paul Wood³ has used the designation "Da Costa's Syndrome," partly to honor Da Costa, but also with the implication that the syndrome may possibly "become of historical interest only." There is in general a justifiable objection to the introduction of a patronymic name into the nomenclature if a more descriptive or specific one can be devised. Temporarily a patronymic name may be adopted, but only until such a time as the nature or etiology of the disease or disorder is clarified. Some of the other terms used to designate this condition are:

1. Effort Syndrome (Lewis)
2. Musculature Exhaustion of the Heart (Hartshorne)
3. X-Disease (Mackenzie)
4. Cardiovascular Neurosis (Caughey)
5. Neurasthenia Cordis
6. Orthostatic Tachycardia
7. Vasoneurosis (used especially for children)
8. Dilatative Weakness (used for adolescents)
9. The Soldier's Heart.
10. Autonomic Imbalance (Kessel and Hyman)
11. Die Herzneurose (of the German authors)
12. Disordered Action of the Heart ("D.A.H." of the British Army).

In 1918 we⁴ suggested the term neurocirculatory asthenia and this was selected because it was descriptive, non-committal as regards the heart, and shortened to the cryptic "N.C.A." would be understood and

not misunderstood all along the line. It may be preferred to the effort syndrome with its possible implication that the symptomatology is that of an exaggeration of the normal response to physical effort. The very varied clinical picture presented by neurocirculatory asthenia probably represents something fundamentally different than the enhanced physiologic reactions to physical exertion, although there are many points of superficial resemblance. Neurocirculatory asthenia has been adopted by the U. S. Army and also for the forthcoming edition of the Standard Classified Nomenclature of Disease. It is included in brackets after "Effort Syndrome" in the Nomenclature of Diseases of the Heart published by the New York Heart Association.

Historical: This is not at all a new disorder. It is stated that even Hippocrates realized that palpitation might result from emotion, fright or excitement. The condition certainly occurs in its milder grades in civil life among adults and children, but becomes more intensified, better defined and exceedingly common under military conditions. Its prevalence in the Civil War was first recorded by Hartshorne⁵ and by Da Costa⁶ in 1864; the latter included it in the first edition of his textbook on "Medical Diagnosis" in 1864, but he waited until 1871 before he finally published his classic paper "On the Irritable Heart: a Clinical Study of a Form of Functional Cardiac Disorder and Its Consequences."⁷ This still stands as a model of direct clinical observation. By following the subsequent histories of his cases over a period of years he collected some fifteen instances in which he thought the irritable heart was followed by cardiac hypertrophy. Da Costa cited this group to show that "disordered function leads to organic disease," i.e., to hypertrophy of the heart. He described the necropsy findings of one patient who died following an operation for strangulated hernia in which there was left ventricular hypertrophy. At the present time the evidence is against this view that neurocirculatory asthenia leads to hypertension and hypertrophy, although of course any individual with (or without) neurocirculatory asthenia may ultimately develop abnormally high blood pressure. Da Costa also included some doubtful or mixed cases—that is patients in whom the symptoms of the irritable heart were superimposed upon those of an organic cardiac condition. He realized that one may have the combination of an irritable heart and valvular disease of the heart. He also took up the differential diagnosis of the irritable heart and pulmonary tuberculosis, anemia and malingering. Hartshorne

(1864) excluded anemia or scurvy (both of which were prevalent among the soldiers of the Army of the Potomac) as etiologic factors in neurocirculatory asthenia, as the heart affection lasted long after the patients were cured of the anemia or scurvy. As a result of his observations on these soldiers Hartshorne says: "Judging from what I have seen, I think it can hardly be a mistaken opinion that they are entirely unfit for ordinary field service in the Army. No doubt many, perhaps most of them, would be quite able to do light service in various ways." Those conclusions of 1864 hold today, although one cannot accept Hartshorne's theory, that the condition is due to a "muscular exhaustion of the heart."

Da Costa found some reference to the condition in the British Blue Book of the Crimean War, and the disorder is mentioned by MacLean⁸ in 1867, by Myers⁹ in his volume "On the Etiology and Prevalence of Diseases of the Heart among Soldiers" (1870), by Tyson¹⁰ during the South African War, and by Captain McCarthy¹¹ in soldiers returned from a campaign on the Indian frontier in 1898. These authors were apt to lay great stress on the accoutrements and tight tunics, and even the busby as a cause of the condition. Its prevalence in a severe form in the British, French and German armies during the first World War was accounted for by the conditions of modern warfare at that time—prolonged marching, trench life, intensive fighting, terrific bombardment, gassing, burial, and trench fever, dysentery and other infections.

What is neurocirculatory asthenia? It seems to me that an abnormal reactivity of the nervous system, including the innervation of the entire circulatory system may account for the varying neuro-psychosomatic symptoms. The symptoms are physiological and psychological.¹² This irritability or instability of the nervous system may originate in an increased stimulation of the cerebral cortex. From the cortex the stimuli may pass to the hypothalamus which is a center for the autonomic nervous system. The hypothalamus is connected on the one hand with the cortex and on the other hand probably with the vagal nuclei and the sympathetic. So, disturbances in the hypothalamic region may affect respiration, pilomotor reflexes, vasomotor reflexes, sudomotor and other reflexes. In this way one may explain to one's self the great variety of symptoms of neurocirculatory asthenia, some of them characteristic of vagotonia, some of sympathicotonia. That is one possible mechanism. Another possible mechanism is the humoral, but this seems less likely.

Further pharmacological studies with adrenergic and cholinergic drugs may help to elucidate the problem.

The thesis that there are situational factors that will produce neurocirculatory asthenia in the individual because of a basic attitude toward that situation is tenable. Given a set of disagreeable circumstances such as warfare, threat of war, or merely drafting, why do some individuals present these symptoms? Partly because some are constitutionally more susceptible as will be shown later, but in addition there are other factors, such as motive. Indeed one does not have to resort to deep psychoanalytical investigations to uncover these latent conflicts. Just superficial consideration will detect emotional attitudes that can give rise to conflicts. If for example a man feels that he is enlisting in a cause for himself or his family, and that there is no alternative, or the alternative is even worse, then there is no conflict. If he is compelled to go to war against his own inclinations, then there may be a conflict and there is a basis for an anxiety state. Neurocirculatory asthenia seems to me to be the somatic component of a psychosomatic state. The more severe the neurocirculatory asthenia, the more it is an expression of visceral rather than of an articulate protest. Pre-war and war conditions make manifest symptoms referable to the cardiovascular system, just as they produce gastrointestinal symptoms, e.g., nausea, vomiting or diarrhea, genitourinary symptoms such as polyuria, and respiratory and sudomotor symptoms. There are undoubtedly many anxiety neuroses that have no somatic manifestations. Neurocirculatory asthenia is important because it ear-marks those men who are potential candidates for an anxiety neurosis or psychoneurosis. You may well ask, if neurocirculatory asthenia is merely a manifestation of a psychoneurotic state, why not turn the examination of registrants, draftees and recruits over to the neuropsychiatrists? It seems, however, preferable to leave the field of diagnosis in the hands of cardiologists and internists, as they are better equipped to rule out such organic diseases as early organic heart disease, pulmonary tuberculosis, the *formes frustes* of Graves' disease and anemia.

Family History and Previous Personal History; Psychoneurotic Factors: To corroborate the view that neurocirculatory asthenia is the somatic concomitant of anxiety and other psychoneuroses there is the evidence which the late Dr. Rothschild and I collected under Sir Thomas Lewis at Colchester in 1917. A comparison was made of the percentages of

TABLE I

PERCENTAGES OF CHARACTERISTICS NAMED IN FAMILY HISTORY OF PATIENTS SUFFERING FROM (1) NEUROSES, (2) "IRRITABLE HEART" OF SOLDIERS, AND (3) CONTROLS

| | <i>Neurosis Per Cent</i> | <i>Irritable Heart Per Cent</i> | <i>Controls (Wounded) Per Cent</i> |
|---|------------------------------|---|--|
| Nervousness | 64 | 45 | 15 |
| Alcoholism (Parents and Grandparents) | 50 | 15 | 24 |
| Teetotalers (Parents and Grandparents) | 30 | 15 | 16 |
| Irritability of Temper | 36 | 27 | 12 |
| Insanity | 34 | 23 | 0 |
| Epilepsy | 30 | 15 | 0 |
| *Tuberculosis (Immediate Family) | 12 | 13 | 4 |
| *Tuberculosis (Relatives) | 5 | 15 | 4 |
| Stigmata | 10 | 17 | 0 |
| Positive History for One or Several of Foregoing... | 74 | 56 | 38 |

*Tuberculosis in the family history would probably not be included if such statistics were being collected today. Similarly nowadays the item "Married" would be omitted from Table II, although it is interesting to find the low percentage of married men among the neurocirculatory asthenics.

certain characteristics in the family history of soldiers suffering from (1) Psychoneurosis, (2) neurocirculatory asthenia or as it was called in 1917, the "irritable heart of soldiers," and (3) controls, i.e., soldiers invalided for war wounds. A positive family history of one or several of the characteristics selected was obtained in 74 per cent of the neuroses group (by Wolfsohn¹³), in 56 per cent of the neurocirculatory group, and in 38 per cent of the controls (see Table I). In the previous personal histories the contrast is much greater. There was a positive personal history in 76 per cent of psychoneuroses, 51 per cent of neurocirculatory asthenia, and only 12 per cent of the controls. A positive family *and* personal history was obtained in 70 per cent of the neurosis group, in 46 per cent of the neurocirculatory asthenias, but in only 6 per cent of the controls (See Table II). The practical military point was this: In such patients invalided for neurocirculatory asthenia as have neuropsychic factors in their family and previous personal histories, the

TABLE II

PERCENTAGES OF CHARACTERISTICS NAMED IN THE PERSONAL HISTORY IN CASES OF (1) NEUROSIS, OF (2) "IRRITABLE HEART" OF SOLDIERS AND OF (3) CONTROLS, I.E., WOUNDED

| | <i>Neurosis Per Cent</i> | <i>Irritable Heart Per Cent</i> | <i>Controls (Wounded) Per Cent</i> |
|--|------------------------------|---|--|
| Stigmata | 34 | 12 | 4 |
| Previous Nervousness | 66 | 46 | 12 |
| Fears | 50 | 31 | 8 |
| Head Injury | 38 | 5 | 12 |
| Epilepsy and "Fits" | 8 | 5 | 0 |
| Tobacco (excessive) | 8 | 1 | 4 |
| Alcohol (excessive) | 6 | 0 | 16 |
| Alcohol (teetotaler) | 48 | 36 | 20 |
| Married | 42 | 18 | 28 |
| Moody | 55 | 27 | 8 |
| Previous Breakdown | 2 | 21 | 0 |
| Enuresis | 12 | 14 | 4 |
| Frights in Childhood | 4 | 19 | 0 |
| Excessive Religion | 6 | 6 | 0 |
| Positive Personal History | 76 | 51 | 12 |
| Positive Family and Personal History | 70 | 46 | 6 |

value of the combatant service rendered in the past is found to be negligible. They are the group who in civilian life usually do sedentary or light work.¹⁴

Constitutional Asthenia: A history of constitutional physical asthenia was obtained in about 70 per cent of this group with psychoneurotic factors. By this rather vague term, "constitutional asthenia," is meant a relative inferiority or an anomaly in the assemblage of inherent characteristics, both functional and morphologic, which go to make up the organism. One may include in this term those who have always been short of breath, have been unable to play the more strenuous games, have fainted or become dizzy readily, have flushed easily, perspired too profusely and suffered from cold blue clammy hands. In addition one

may add those who have certain forms of "habitus," such as the splanchnoptotic, the feminine, the eunuchoid; the flat chested, reedy type, and those with drop hearts.

Juvenile Vasoneurotics: Bass and Wessler¹⁵ in 1913 were the first American clinicians to draw attention to a group of children presenting the symptoms of neurocirculatory asthenia, who in addition showed orthostatic albuminuria. In 1918 we were able to show that a considerable percentage of soldiers invalided for neurocirculatory asthenia had shown symptoms of constitutional asthenia before the age of seventeen. In other words, many patients with neurocirculatory asthenia are the adult individuals who during their developmental period presented vasoneurotic symptoms. Some in this group had had symptoms as long as they could remember, but usually the symptoms of this constitutional weakness manifested themselves between the ages of eight and sixteen years. Since then we have seen many instances in civilian practice of children suffering from this condition, some of whom have continued to suffer into adult life. The natural history of this disorder from childhood to adult life and even old age requires further investigation and description.

Clinical Picture: A clinical description of this disorder as it occurs in its mild form among civilians, for example after influenza, is hardly necessary because it is familiar to general practitioners. It was a memorable picture, however, to see the severe and incapacitating type of the same disorder at Colchester among British soldiers, invalided from France in 1917-18. Many arrived on stretchers, completely done in physically and psychically. Their predominant symptoms could be referred to the circulatory and nervous systems. They complained of dyspnea, palpitation, chest pain, extreme fatigue, dizziness, nervousness and headaches; and this was the order of frequency of their chief symptoms. We were struck by the cold blue clammy hands, by the axillary sweating, the presence of a coarse tremor which sometimes amounted to a shivering, although they were not cold. There was a great variety of other subjective symptoms such as sleeplessness, paresthesias, perspiration, feeling of faintness or actual syncope, anorexia, diarrhea, and tremor. There was a striking disproportion between the severity and number of the subjective symptoms when compared with the objective signs of neurocirculatory asthenia. The general appearance of these invalids with their anxious faces, asthenic bearing, trembling, cold blue

(Anglican) hands, dyspnea, diffuse cardiac apical impulse, hyperesthesia of the skin or muscles of the chest wall, and the exaggeration of many of these signs and symptoms on effort, made the diagnosis easy in most instances. It should be emphasized that the diagnosis could usually be made on positive evidence, and not merely by the exclusion of organic or neuropsychiatric conditions. It was at times amazing to see these same soldiers, forced out of bed and obliged to take graduated exercises for a period of weeks, return to high grades of physical exercise and to military duty. In exceptional instances the diagnosis was doubtful for weeks, and was helped by the results of the therapeutic test of physical training under the scientific direction of Sir Thomas Lewis.

Electrocardiographic Abnormalities: Paroxysmal tachycardia, premature beats, and sinus arrhythmia are well known to occur in the course of neurocirculatory asthenia. Very exceptionally there are also prolongation of the P-R interval, changes in the QRS complex, and especially inversion of T_2 and T_3 (Graybiel and White¹⁶). Only recently it has been shown that pure fear can temporarily produce such changes in the electrocardiogram, resembling somewhat changes seen in coronary insufficiency.¹⁷

Diagnosis: (a) Pulmonary Tuberculosis: Here the group at Colchester undoubtedly made their greatest mistakes, for in the afterhistories of six hundred and one men followed to the fifth year by Grant,¹⁸ twenty-two were finally diagnosed as pulmonary tuberculosis, which is an incidence 80 per cent greater than pulmonary tuberculosis in the general population of London over the same period. It must be mentioned that we were working in barracks without any X-ray machine, and it emphasizes the well-known fact that such mistakes are inevitable if routine chest X-rays are not taken.

(b) Graves' Disease: Contrary to what might be expected by those who still consider neurocirculatory asthenia a pre-Graves' state, the differential diagnosis is usually not very difficult. It is admitted that neurocirculatory asthenia and Graves' disease are probably related—perhaps cousins once removed—but Graves' disease has some unknown X-factor not present in neurocirculatory asthenia. The best single diagnostic criterion is of course the increased metabolic rate. In neurocirculatory asthenia the basal metabolic rate if really basal is within the normal range, as was demonstrated at Lakewood years ago by Peabody, Wearn and Tompkins.¹⁹ Other useful diagnostic points are the general

hyperkinetic manner of the Graves' patients, the *warm* rather pink hands of Graves' disease, the persistence of tachycardia in sleep, the presence of characteristic eye symptoms, and the favorable response to iodine administration. In regions of endemic goiter, for example the north-western part of the United States, one used to see many recruits who had the combination of simple goiter and neurocirculatory asthenia. How many of these eventually developed Graves' disease I do not know, but of the six hundred and one Colchester patients, not one developed Graves' disease within the five year period in which they were followed.¹⁸

(c) Early Organic Valvular Disease: There is real difficulty in differentiating early mitral disease and neurocirculatory asthenia. A history of rheumatic fever or chorea is not very helpful as it occurred in at least 65 per cent of the cases of mitral stenosis and in 23 per cent of the effort syndrome soldiers. A systolic murmur, accentuated first apical sound, accentuated second pulmonic sound and tachycardia may occur in either condition. One may have to examine the patients repeatedly after effort, before one is able to elicit a presystolic or diastolic murmur, a true thrill, or definite cardiac enlargement. Sometimes a cardinal physical sign, the presystolic murmur, can be brought out by auscultation immediately after exercise or by laying the patient in the supine or left lateral position. Unfortunately the symptoms of neurocirculatory asthenia are frequently superimposed upon those of organic heart disease. One should remember that neurocirculatory asthenia alone may be characterized by dyspnea, pain, palpitation, cyanosis, syncope, fatigue, dizziness—all of which also occur in heart failure, but usually not until the cardiac insufficiency is advanced.

(d) Rheumatic Cardiac Disease: In children one is frequently faced with the very practical problem of differentiating between a vasoneurosis with fleeting pains and perhaps fever due to some accidental complication, and true rheumatic carditis. Rheumatic fever may be diagnosed and the child sent for years at great sacrifice to the South or California. There may be all the symptoms and signs of neurocirculatory asthenia plus evidence of an infection, and still that infection may not be rheumatic fever, but a chronic pyelitis or a sinusitis. Further, even if the rheumatic state is demonstrated by definite clinical evidence such as polyarthritis, even then no permanent harm is done, unless the heart becomes involved. One should watch closely for definite evidence of

cardiac involvement, that is cardiac enlargement, a presystolic or diastolic murmur, pericarditis, or positive electrocardiographic evidence, before jumping at the diagnosis of rheumatic cardiac disease. As it is impractical to send all children suspected of rheumatic carditis for years to a climate where streptococcus infections are rare, I have tended to limit such radical advice to those who have had at least one proven attack of rheumatic infection or in whom actual rheumatic carditis has been established. There are many cases of acute rheumatic fever or chorea in which ultimately no evidence of cardiac involvement can be proven. The prophylactic treatment for rheumatic recurrences with sulfonamides is promising.

(e) *Hypertension*: In taking the blood pressure of registrants and volunteers and also of patients with neurocirculatory asthenia one encounters, not infrequently, blood pressure readings above 155 mm. of mercury for the systolic and 90 or above for the diastolic pressure. Almost every week I run across registrants with neurocirculatory asthenia and a systolic blood pressure of 180. Are these examples of essential hypertension? The majority are not, and it is probably for this reason that the examiners for the selective draft are not instructed to take blood pressures. In most instances it is the excitement which elevates the blood pressure to the figure of 150 or over. If one takes the same individual's blood pressure at home while at ease, the pressure is usually found to be within normal limits. Finding the increased blood pressure is of value in directing attention to the necessity of searching for other signs of cardiovascular or renal disease such as cardiac hypertrophy, ringing aortic second sound, or fundus changes. Paul Wood²⁰ using the Hines cold pressure test on twenty-five cases of neurocirculatory asthenia came to the conclusion that 90 per cent of these were not instances of incipient hypertension. Grant¹⁸ apparently found no evidence of increased hypertension in his study of six hundred and one cases of effort syndrome followed up for five years. It is still a question in my mind whether many of these youths with labile blood pressures and a tendency to elevation, will not prove to be subjects of essential hypertension in middle life. It is important to get a more definite statistical answer to this practical question. Meanwhile it should be noted that the latest statistics of the selective draft in New York City show 2,978 rejections for persistent high blood pressure out of 115,569 registrants examined.

(f) *The differential diagnosis* of neurocirculatory asthenia from

TABLE III

AFTER-HISTORIES OF "EFFORT SYNDROME" CASES RETURNING TO CIVIL LIFE AFTER THE GREAT WAR. STATE AFTER FIVE YEARS: PERCENTAGE FIGURES (AFTER GRANT¹⁸)

| <i>Number of cases</i> | <i>Fit</i> | <i>Improved</i> | <i>Stationary</i> | <i>Worse</i> | <i>Incidence of serious disease</i> | <i>Dead</i> |
|------------------------|------------|-----------------|-------------------|--------------|-------------------------------------|-------------|
| 601 | 15.3 | 17.8 | 56.2 | 3.2 | 8.7 | 2.3 |

anemia, angina pectoris, epilepsy (petit mal), toxic myocarditis and malingering cannot be gone into. After a year's experience in a medical advisory capacity with the selective draft, I may say that many registrants may have overemphasized their symptoms, but I have run across only one instance of deliberate malingering and that was detected.

Prognosis: The question of prognosis should be divided into (1) the immediate prognosis of soldiers invalided for neurocirculatory asthenia, based on their response to graduated physical exercise and (2) the ultimate after-war prognosis of such soldiers when they return to civil life. Under the direction of Lewis² the grading of men leaving the Military Hospital at Colchester was as follows:

| | |
|---|-------------|
| Fit for general service | 20 per cent |
| Fit for hardening or labor | 30 per cent |
| Fit for light or sedentary work | 30 per cent |
| Permanently unfit | 20 per cent |

This categorization generally proved to be correct as tested by the subsequent military careers of these soldiers discharged from the hospital. Our knowledge of the ultimate prognosis of soldiers after their return to civil life rests entirely on the follow-up study made by Grant¹⁸ on six hundred and one soldiers for five years after their discharge to civil life (Table III).

Grant adds that this general prognosis is modified by the age of the patients and the tolerance to exercise. Thus the percentage of those between 17 and 20 years who were finally classified as fit was 25 per cent, whereas it was only 2.1 per cent for those between 41 and 50 years. In the same way the percentage of ultimate recoveries paralleled the grouping based on exercise tolerance, that is, the better the patient's tolerance to exercise, the greater were his chances of ultimate recovery.

You may be interested in the latest statistics of the medical findings

among registrants in the New York City area for the Selective Service Draft, for which I am indebted to Colonel S. J. Kopetzky and Dr. Arthur M. Tiber. There were 115,569 registrants examined. For diseases of the heart, blood vessels and circulation 12,261 or 10.61 per cent were rejected. For neurocirculatory asthenia 195 were rejected by the examiners, that is 1.6 per cent of the cardiovascular cases. Of course, many instances of neurocirculatory asthenia have been rejected under the caption of tachycardia (1,180 registrants) or of one of the psychoneuroses. I venture to state that many potential cases of neurocirculatory asthenia have slipped through and many of these may give adequate service without being disabled. To this day of course we do not know how many cases of neurocirculatory asthenia went through the first Great War, gave valuable service, and were never heard from by medical officers. As you are aware, neurocirculatory asthenia cases, unless mild, are entirely disqualified by the Draft Board and put into Group 4F. If mild, they are accepted in Group 1A, for full duty.

Treatment: The treatment may be divided into (1) preventive and (2) curative. The latter consists in attempts at physical and psychological rehabilitation of the individual; this is best accomplished by the collaboration of cardiologists and neuropsychiatrists.

Preventive Treatment: It is important to allow a proper convalescent period after any infection or severe operation. After complete recovery, patients should be gradually hardened before returning to full duty.

2. Neurocirculatory asthenia is due in part at least to emotional disturbance, especially fear. Therefore the cause for the emotional upset should be removed; but if this is impossible, the individual should be assisted to make an adjustment. The medical officer can sometimes stop the bullying non-commissioned officer from precipitating neurocirculatory asthenia; if not, he may adjust the recruit to this hardship and to his fear of army life.

3. Neurocirculatory asthenia should be recognized as early as possible, especially in children, and measures taken to prevent the condition from becoming chronic or permanent. In potential cases, i.e., those with family and previous personal histories of neuropsychic factors, psychic insults should be prevented or removed. The famous psychologist, William James, years ago in "A Moral Equivalent of War" advocated that every youth should serve the nation for a term of years in an industrial army. This would harden lads, teach courage and heroism, and would

probably help the younger generation to adjust themselves to life.²¹

Curative Treatment: 1. There is no specific treatment.

2. The condition should be explained at the first interview and the patient reassured that he has no organic heart disease.

3. Lewis² used daily graduated physical exercises with route marches over a period of five or six weeks. The results were fairly good, but it was difficult to tell whether it was the physical exercises themselves or the psychotherapeutic effect of the latter which accomplished the relatively good results. For civilians, graduated moderate physical exercise is to be recommended, such as golf, bicycling, pingpong, or swimming. The mere permission to indulge in exercise frequently convinces the patient that he has no organic cardiovascular disease.

4. Occupational therapy has made great strides since 1917, and should be of value, if only to prevent invalids from becoming depressed. Carpentry, metal work, leather work, drawing, modelling and painting will afford regular occupation for men with neurocirculatory asthenia for at least half the day.

5. Psychotherapy is indicated, but the psychotherapist must individualize and even then be prepared for dubious results. Attempts with psychoanalyses were not successful at the Military Hospital in Colchester, but Captain Rivers who attempted psychoanalysis admitted he could not get far with privates and believed he would have been more successful with officers. Suggestion, including hypnotism, has been used in relatively few cases which were diagnosed as hysteria. Patients should be relieved of any unusual responsibility until they have recovered.

6. Removal of foci of infection in teeth, tonsils, intestinal tract, including the appendix and gallbladder, may or may not be of service.

7. Sedatives may be used to tide over periods of insomnia or excitement. Other medication, except for individual symptoms, such as constipation, is useless. Amphetamine sulphate (benzedrine) seems to help the asthenia while it is being taken.

8. In civilian practice vitamins should be tried, although there is at present no evidence of a primary vitamin deficiency in the etiology. In almost any chronic disorder there may be a secondary clinical or sub-clinical vitamin deficiency, due for example to loss of appetite. Nicotinic acid has been especially vaunted for the psychoneuroses by competent neurologists. The administration of nicotinic acid in adequate doses certainly results in vasodilator phenomena which may have a beneficial

psychic effect. However, Jolliffe has given as much as 1000 mgm. of nicotinic acid a day for eight days, followed by 300 mgm. a day for a month, without making any impression on neurocirculatory asthenia. With the present army daily ration consisting of 4,500 to 5,000 calories and rich in vitamins, one would not anticipate any vitamin deficiency among soldiers.

9. Adrenal denervation and ganglionectomy for neurocirculatory asthenia: It occurred to Crile²² some years ago to treat those cases which are resistant to medical management by breaking the brain-adrenal-sympathetic chain at the adrenal glands by denervation, or at the celiac ganglion by ganglionectomy. "Of one hundred and fourteen cases of neurocirculatory asthenia treated by adrenal denervation and followed up, in one hundred and seven cases or 93.86 per cent, the condition was cured or improved." Of fourteen cases subjected to celiac ganglionectomy and section of some communicating branches to the adrenal medulla, thirteen were followed up; "in twelve of these, or 92 per cent the condition was improved or cured. There was only one failure." These are remarkable results.

If these therapeutic suggestions are followed, there is a fair prospect of a return to full or partial military duty of some patients, of economic restitution in civil life of others, and of symptomatic amelioration of the remainder who are permanently incapacitated for any real work. In the treatment of neurocirculatory asthenia in times of war, it is to be remembered that it is to the soldier's advantage to exaggerate and prolong his complaints. The medical officer may be torn between his obligation to the soldier as an individual and his duty to the State.

CONCLUSION

Neurocirculatory asthenia in its severe incapacitating form is a neurosis and usually a war neurosis frequently on a constitutional basis. It represents the somatic component of a psychoneurotic state. Its detection is now particularly important because it ear-marks those who are potential candidates for a neurosis under war conditions. It is estimated that over half of the beds in military hospitals are now occupied by patients with nervous or mental disorders,²³ thus permanently depriving others of these hospital facilities. It behooves us therefore to study this disorder, neurocirculatory asthenia more intensively, to prevent its occurrence in all the services if possible, and to learn to relieve the

condition promptly when it occurs.

It is particularly appropriate that Americans should pursue these investigations, as the classic description of the disorder was based on observations made during our own Civil War by a Philadelphia clinician, Dr. J. M. Da Costa.

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THE PRESENT STATUS OF THE DIAGNOSIS
OF UNCOMPLICATED SYPHILITIC AORTITIS*

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I n the last 15 years a large amount of work has been done on problems relating to cardiovascular syphilis. Some of this has been fruitful but in at least two fields considerable remains to be done, namely, in the early diagnosis of uncomplicated aortitis and in the efficacy of treatment. Our discussion will be limited to the problem of the diagnosis of uncomplicated aortitis. By this term we mean syphilitic involvement of the aorta in the stage preceding the development of aortic insufficiency, aneurysm or syphilitic coronary ostial stenosis.

In 1932 Moore¹ studied the clinical records of 105 cases of uncomplicated syphilitic aortitis which had been discovered at necropsy at The Johns Hopkins Hospital between the years 1910 and 1930. Only 4 had been diagnosed ante mortem and in only 13 others had the diagnosis been suspected. In 1927, in The Brooklyn Hospital Adult Cardiac Clinic we undertook to examine and follow all syphilitic patients enrolled in the Venereal Disease Clinic. By 1935² a diagnosis of uncomplicated syphilitic aortitis had been made in 59 (17.05 per cent) of the 346 patients included in the study. In contrast to this, White and Wise³ in 1937 stated: "Since a clinical diagnosis of aortic syphilis can rarely be made within ten years after infection, it may safely be said that the early diagnosis of cardiovascular syphilis is practically impossible. If this is so, our interest is naturally next concentrated on the problem of the earliest possible diagnosis of such disease."

Because of conflicting statements, it seems desirable to attempt to throw more light upon the difficult problem of the diagnosis of uncomplicated aortitis. Since it is agreed by most pathologists that syphilis can affect the aorta soon after the primary infection, it becomes important to know in what proportion of patients this complication occurs.

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Langer⁴ found that from 70 to 80 per cent of all syphilitic patients who came to necropsy at the Rudolf Virchow Krankenhaus presented evidence of involvement of the aorta. Moore, Danglade and Reisinger¹ placed the figure based on evidence collected in this country and abroad at between 80 and 90 per cent. Of course this does not imply that syphilitic aortitis was the cause of death in all these patients or that it caused cardiac symptoms. It means only that a syphilitic lesion of variable extent was present in a large per cent of all syphilitics examined post mortem. Furthermore, these statements do not take into consideration the very important factor of treatment. Vonderlehr and Usilton⁵ have shown that adequate treatment, given at the time of the chancre and continued for 2 years thereafter, prevented the development of cardiovascular syphilis in a group of syphilitics observed 10 or more years after the infection. Therefore we must suspect the probability of aortitis in all syphilitics except in those who have had early and adequate treatment.

By what means can the physician arrive at a diagnosis of uncomplicated syphilitic aortitis? In the first place, he must not wait for cardiac symptoms to call his attention to the aorta because uncomplicated syphilitic aortitis is a symptomless disease. Wilson,⁶ in an analysis of 211 cases of syphilitic aortitis proven at autopsy, found that cardiac symptoms were related to the development of the complications of aortitis or to some other cardiovascular lesion. If we wait until the patient comes to us complaining about his heart we will not see him until aortic insufficiency, aneurysm or coronary osteal stenosis has appeared. This statement brings to mind the symptom "aortalgia," the burning pain behind the upper sternum said to be caused by syphilitic inflammation of the aortic wall. In the fourteen years of our study we have not encountered this symptom but we have met the anginal syndrome often. It seems probable that aortalgia was the name given to the pain of coronary insufficiency before the existence of syphilitic coronary osteal stenosis was well known. If a patient with syphilitic aortitis complains of retrosternal or precordial pain on effort, we add the diagnosis syphilitic coronary osteal stenosis. However, the converse of this is not true. von Jagic and von Zimmermann-Meinzingen⁷ in a clinical and necropsy study found the anginal syndrome in only 50 per cent of the patients in whom syphilis had involved the coronary arteries. Syphilitic coronary osteal stenosis may produce sudden death without previous symptoms.

In diagnosing uncomplicated syphilitic aortitis there are two physical signs that may be helpful. The first is a hollow accentuated aortic second sound. We have not been able to discover any quality in this that is characteristic of syphilitic aortitis. Hypertension and arteriosclerosis may cause the same phenomenon. Nevertheless the following rule may be helpful: In a patient under 40 without hypertension who has a hollow accentuated aortic second sound, suspect aortic dilatation due to syphilis.

The second physical sign is a systolic murmur at the aortic area. There is nothing pathognomonic about this because it is also found in arteriosclerosis and hypertension but it does serve to call attention to possible changes in the caliber of the aorta or in the elasticity of its wall.

Widened retromanubrial dullness has been given as a sign of a dilated aorta. Unfortunately slight or even moderate changes in the size of this vessel cannot be detected by percussion. Only when there is great dilatation can it be demonstrated by this method. I do not mean to imply that the practice of percussion of the base of the heart and great vessels should be abandoned, because the method may detect aneurysmal dilatations, but it should not be included in the criteria for the diagnosis of uncomplicated aortitis.

Fluoroscopy, orthodiagraphy and teleoroentgenography are very useful in studying the size and shape of the aorta and should be used periodically in every patient who has had syphilis. We should never fall into the error of treating a patient with syphilis of the central nervous system, for example, for months or years and forget to have a look at his aorta in the fluoroscope. Before arriving at a judgment it is necessary to be familiar with the size, shape and position of the normal aorta. Laubry⁸ has carried out some valuable studies that give much information on these points. A cadaver was suspended by the head, a radiopaque substance was injected by way of the carotid artery into the aorta and heart, thereby filling the left ventricle and auricle. Roentgenograms were taken of the heart and great vessels. The material was then washed out and a fresh supply injected by way of the superior vena cava into the right auricle, right ventricle and pulmonary artery. Roentgenograms were taken of these structures. By superimposing the two sets of films the topographical anatomy of the heart with the body in the erect position could be studied. Laubry demonstrated conclusively that in young subjects the aorta is a midline structure situated behind

the body of the sternum, rising vertically toward the neck and then curving backward and slightly to the left. The right border of the vascular pedicle is formed by the superior vena cava. As age advances, the aorta elongates, the loop widens and the ascending aorta moves to the right pushing the superior vena cava to the right at first and later backward so that in older subjects the aorta comes to form the right border of the vascular pedicle. All Laubry's work was perforce done after death when anatomical relations may be different from what they are in life. Cosseo⁹ of Buenos Aires has supplied the final proof that Laubry's observations hold true for the living as well. In a patient under fluoroscopic observation he inserted a long rubber catheter through the right median basilic and subclavian veins, down the superior vena cava and into the right auricle. By this daring experiment he showed that the superior vena cava lay to the right of the aorta.

With these concepts in mind and having familiarized ourselves with the appearance of the normal aorta, the next step is to learn to recognize the characteristics of a dilated vessel. Early in our studies of cardiovascular syphilis we attempted to use the width of the vascular pedicle measured by the Vaquez method as a criterion. On the basis of Bainton's¹⁰ work we set 7 cm. as the upper limit of normal for the vascular pedicle at any age. Whenever this measured more than 7 cm. we considered it to indicate widening of the aortic loop. Teleoroentgenograms were taken year after year on every patient. When these were reviewed in chronological order it was found that there was considerable variation in the width of the vascular pedicle in either direction in the same patient. With our present radiologic technique it is not possible to synchronize the making of the exposure with a given phase of the cardiac cycle. As a result some films are exposed when the aorta is distended by systole and others when it is contracted in diastole. Another source of error is the centering of the patient. If this is not exact there will be a change in the measurement of the vascular pedicle. The level of the diaphragm is another variable, being altered by changes in body weight or in the phase of respiration at which the film is exposed. As time went on we came to see that we could not be certain of the upper limit of normal for the width of the vascular pedicle and from this to conclude that a measurement in excess of a given figure indicated a dilated aorta. Consequently we have abandoned our original criterion of 7 cm. as the upper limit of normal and rely upon information that can be gained

through a study of the contours of the aorta in the teleoroentgenogram and under the fluoroscope. Localized bulging of the wall of the aorta, particularly to the right in the ascending portion or forward on the ventral surface can be interpreted as indicating a weakening of the wall. Under these circumstances the aorta may be said to be dilated. Again, if there is general widening of the vascular pedicle to such a degree that its right border extends as far as the right border of the heart, it is safe to assume that aortic dilatation is responsible for this, provided that abnormalities of the lungs, pleura and mediastinum have been excluded. Abnormal pulsations either localized or diffuse, if they are well marked, indicate dilatation of the aorta. When the patient is viewed in the left oblique position, the ventral surface of the normal aorta extends toward the neck in a straight line or in a gentle forward curve. A sharp bend forward indicates dilatation or elongation of the aorta.

Attempts to measure the actual diameter of the aorta, either in the ascending portion or arch, have met with failure except in those instances where advanced arteriosclerosis outlines the vessel walls distinctly. In either the right or left oblique views the luminosity of the air columns in the trachea and main bronchi make it impossible to locate the aortic walls with any degree of certainty. Kreuzfuchs¹¹ has described an ingenious method of measuring the true diameter of the aorta at the knob which has proved valuable in our hands. Under fluoroscopy with orthodiagraphic technique the left border of the knob of the aorta is found and marked on the screen. The patient then swallows thick barium paste which he has been holding in his mouth. As the column descends in the esophagus to the right of the aortic knob a crescentic indentation will be seen in it formed by pressure upon the esophagus exerted by the aortic arch at the knob. The central point of this crescent is then marked on the screen. The distance between these two points after 2 mm. has been subtracted for the thickness of the esophageal wall is the true diameter of the aortic knob. Roesler¹² gives 2.0 and 4.0 cm. as the minimal and maximal figures for healthy adults.

When all these methods of roentgen examination have been used, it is possible for the experienced roentgenologist to state whether there is evidence of aortic dilatation or not. However, we do not believe that it is possible for him to make a diagnosis of syphilitic aortitis on x-ray evidence alone. The clinician must decide what disease or combination of diseases is responsible for the dilatation of the aorta.

Having discussed the clinical and roentgenologic aspects of the diagnosis of uncomplicated aortitis, it is possible to derive six diagnostic criteria* therefrom:

1. The patient must be 40 years of age or younger. Ophüls¹³ in a statistical survey of 3000 autopsies found that between ages 30 and 40 arteriosclerosis was slight and appeared in only 6 per cent of the cases whereas between 40 and 50 nearly one fourth of all cases showed vascular lesions. It is therefore impossible for the clinician to say whether syphilis or arteriosclerosis or a combination of both is responsible for changes in the aorta appearing after the age of forty.

2. The patient must have had syphilis beyond reasonable doubt. In our studies we have required a history of an initial infection plus one strongly positive Wassermann reaction or, if there is no history of infection, then two strongly positive Wassermann tests. If neither of these is present then there must be incontrovertible evidence of syphilis elsewhere in the body; tabes, for example. If one attempts to discover syphilitic aortitis in a group of patients in some of whom the presence of syphilis is in doubt the percentage incidence will be too low.

3. There must be no evidence of any other disease that might dilate the aorta. Arteriosclerosis, rheumatic fever, rheumatic heart disease, hypertension and hyperthyroidism must be excluded.

4. There must be roentgenographic or fluoroscopic evidence of a dilated aorta.

5. There may be a hollow, accentuated aortic second sound.

6. There may be a systolic murmur at the aortic area.

Hedley¹⁴ has recently published almost identical criteria except that he includes "a history of cardiac insufficiency, precordial or substernal distress, or paroxysmal dyspnea" as one of them. As already emphasized cardiac symptoms appear late in the course of cardiovascular syphilis and are not helpful in the diagnosis of uncomplicated aortitis. When the results of 8 years of the cardiovascular syphilis study in The Brooklyn Hospital Cardiac Clinic were reviewed in 1935² the criteria for the diagnosis of uncomplicated aortitis were less rigid than at present. The age limit was 50 years and 7 cm. was used as the upper limit of normal for the vascular pedicle. Using these criteria 59 (17.05 per cent) of the 346 patients in the series were diagnosed as having uncomplicated aortitis. Now after 14 years of the study the age limit has been reduced to forty

* These criteria were first published in *The Brooklyn Hospital Journal*, April 1940.

TABLE I

DEVELOPMENT OF GRAVER LESIONS UNDER OBSERVATION

| Diagnosis on First Examination | Number of Cases | Developed Dilated Aorta | | Developed Aortic Insufficiency | Developed Aneurysm |
|---|-----------------------|----------------------------|----------|--------------------------------------|-----------------------|
| | | Before 40 | After 40 | | |
| Potential | 357 | 2* | 4* | 0 | 0 |
| Uncomplicated Aortitis | 8 | | | 0 | 0 |
| Aortitis or Arteriosclerosis of Aorta (over 40) | 55 | | | 5 | 1 |

* In 2 additional cases under 40 and in 27 over 40 aortic dilatation was found by fluoroscopy but we cannot be certain that this developed during the period of observation since there had been no previous fluoroscopic examinations.

and the use of a numerical figure as the upper limit of normal for the vascular pedicle has been abandoned. As the result only 12 (2.5 per cent) of the 477 patients now included in the study are considered to have uncomplicated aortitis.

One way to test the validity of these criteria is to see whether under observation any of the patients develop the graver lesions of cardiovascular syphilis: aortic insufficiency, aneurysm or coronary ostial stenosis. None of the 12 patients (Table I) diagnosed as having uncomplicated aortitis have done so. However, there are 86 patients in the study group in whom the aorta is dilated but who are over 40 years of age. In these a diagnosis of aortitis *or* arteriosclerosis is made because it is not possible to be sure which disease is responsible for the dilatation of the aorta. Among these 86 patients, 5 have developed aortic insufficiency and one an aneurysm.

There are 357 patients diagnosed as potential cardiacs.* They have all had syphilis but when they first came to the cardiac clinic they showed no evidence of cardiovascular involvement. Two of these developed dilated aortas before they reached the age of 40 and 4 afterward. In the 2 still under 40 the diagnosis of syphilitic aortitis is justified but in those over 40 the dilatation must be ascribed either to syphilis or arteriosclerosis.

Before discussing the significance of these data, it must be stated that most of the 477 patients have been receiving antisyphilitic treatment

* According to the criteria of the New York Heart Association.

more or less regularly during their period of observation. This may be one of the reasons for the small number of patients in whom the disease progressed to the point where its late sequelae were manifest. Bruusgaard¹⁵ in a group of syphilitic patients who had never received any antiluetic treatment found that 1.5 per cent had cardiovascular syphilis in from 3 to 10 years after infection and 10 per cent had it after 20 to 30 years.

Another explanation may be that the patients have not been observed over a long enough period. Syphilitic aortitis progresses very slowly so that its late sequelae are not discovered until an average of 20 years has passed after the initial infection. The fact that none of the patients who were under 40 when first observed developed aortic insufficiency or aneurysm while 6 of those over 40 did so seems to indicate that our failure to observe these complications in the younger group is related to the shorter duration of the disease.

Another method of testing the validity of a set of diagnostic criteria is to compare the clinical diagnosis with the findings at post-mortem examination. The difficulty with this method for our purposes lies in the fact that patients with uncomplicated aortitis do not die of this condition and therefore our opportunities for necropsy study are limited to those who have died from other causes. In the past 14 years we¹⁶ have had this opportunity 13 times. In 4 instances in which the clinical diagnosis was "normal aorta" the necropsy diagnosis was the same in 3. In 2 cases diagnosed uncomplicated syphilitic aortitis we were right in one and wrong in the other. There were 7 patients with dilated aortas who were over 40 when this condition was discovered and because of this the clinical diagnosis was aortitis or arteriosclerosis or both. Necropsy confirmed this diagnosis in all 7 cases. It should be pointed out here that a clinical diagnosis including 2 diseases has a double chance of being confirmed post mortem. Nevertheless a group of criteria whose use makes it possible to arrive at a correct clinical diagnosis in 11 out of 13 cases appears to warrant further clinical trial.

CONCLUSIONS

1. The diagnosis of syphilitic aortitis can be made before aortic insufficiency or aneurysm has appeared.
2. The frequency of the diagnosis is not as high as that found in our first report (17.05 per cent). At present it is 2.5 per cent.

3. The measurement of the width of the vascular pedicle by the Vaquez method cannot be used as a criterion of dilatation of the aorta.
4. The diagnosis of uncomplicated aortitis should not be made in patients over 40 years of age.
5. The diagnosis "aortitis or arteriosclerosis" is a useful method of expressing the probable pathology in patients whose aortas are dilated and who are over 40 years of age.

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COAGENCY IN THE APPROACH TO THE PROBLEM OF RHEUMATIC HEART DISEASE*

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WITH but few exceptions, it is almost impossible to trace the origin of those major advances in the discovery and practical application of medical knowledge which have occurred with such rapidity in recent years. The impact of each important scientific discovery and of each demonstrated need upon a receptive mind is no longer the rare privilege of a few, but falls with similar force upon the minds of men in many places. Thus we see the simultaneous growth of otherwise unrelated movements in different parts of the world and of interest in a single problem by different groups or individuals within the same parts of the world.

For example, the fact that by last summer eleven States had, one by one, embarked upon so-called cardiac programs,¹ should not be interpreted as evidence that one State followed the pattern of another, or that they all stemmed from a common source of leadership, but rather as a normal outcropping of accumulated experiences common to persons in all these States and modified in time and form mostly by opportunity in terms of environmental differences. The fact that New York State was one of the last of these eleven, does not in itself, to my mind, single it out as being backward. In fact, quite to the contrary, one might justify the somewhat paradoxical statement that it was advanced and hence felt the need of further progress somewhat more slowly.

The New York Heart Association had developed a highly organized system of cardiac clinics and conducted valuable studies over a period of twenty years;² cardiac clinics of merit were in operation in two other major cities; one-half of the beds for the convalescent care of cardiac children in the country were located in this State;³ cardiac children were extended special educational facilities, subsequently criticized

* Read before a Joint Session of the Section on Pediatrics, The New York Academy of Medicine, and the New York Heart Association, at New York City, February 10, 1942.

though they have been, in New York City;⁴ our medical schools and research institutions had earned important places of leadership in this field; The New York Academy of Medicine and the New York Tuberculosis and Health Association made formal recognition of the need of public education in rheumatic disease some 7 years ago;⁵ and our leaders and thinkers in clinical medicine, research, and public health, had kept pace with those in other parts of the country in pointing out the needs for a comprehensive public health approach to the problem of heart disease.^{2, 6-13} The foregoing, however, must be said with one sweeping reservation. Due credit must be given to the administrative imagination and genius of the minds behind the London Rheumatism Scheme,¹⁴ which has greatly preceded, but for some unaccountable reason, very little influenced our urge to similar action.

Being thus advanced, the more the pity of course, that it took us so long to realize how inadequately we were prepared to make any appreciable inroads upon so large a problem; how insufficient the periods of hospital care being received by children with acute rheumatic fever;² how hopeless the chance of providing adequate convalescent care in which the whole child and his social environment were given consideration;³ how poor our supervision of the cardiac child in school;⁴ how ineffective our facilities for case finding and diagnosis; how lacking the means for coördinating and fully utilizing the services of existing agencies.

Of course these difficulties were recognized by some. The broadened concept of heart disease as a public health problem was voiced by a number of those here this evening several years before our program was undertaken. I can give no better evidence of their forethought than to quote from Dr. Boas,¹⁵ who, in addressing the State Conference of Social Workers in 1935, said: "The State Department of Health must pay more attention to these cardiac cripples. In the past the term cripples has been restricted to children with orthopedic defects, those with paralysis following poliomyelitis or with diseases of the bones and joints. The attention of the State Department of Health has been confined to these cases. The child with heart disease is just as much a cripple as a child with a paralyzed leg and is just as deserving of rehabilitation. Emphasis of this point of view is particularly important at present when under the new Social Security Act the State Department of Health is planning a new study of the needs of crippled children. . . ."

By 1939 and early 1940, these views had grown to a point where they were well supported by medical opinion in general and Doctor Edward S. Godfrey, Jr., State Commissioner of Health, was approached by leaders from this Academy, the New York Heart Association, the American Academy of Pediatrics, two medical schools (one in New York City and one upstate), and the New York City Department of Health, with the suggestion that the time had come when the administrative assistance that the Department could best provide was much needed. This suggestion met with two coincidental and favorable circumstances; namely, the announcement by the Children's Bureau of the United States Department of Labor that certain of the Social Security funds allocated to it for Crippled Children's Services would be made available to aid in State programs for the care of children with rheumatic heart disease, and the availability of 96 beds, then unused, at the New York State Reconstruction Home at West Haverstraw, an institution under the jurisdiction of the Department of Health.

Doctor Godfrey called together two advisory groups of highly qualified physicians to consider and advise him with respect to: First, the propriety of the State's undertaking such a program; and second, the suitability of the State Reconstruction Home for a convalescent hospital service for cardiac children. Both reports were favorable to the proposed action. Accordingly, late in 1940, an administrative unit known as the Cardiac Bureau was added to the Department under the direction of my associate, Doctor David D. Rutstein, and by the early summer of 1941, the necessary personnel had been obtained and the cardiac service was opened at West Haverstraw.

The objectives of the State program and the details of the service at West Haverstraw are, I am sure, familiar to many of you since we have drawn heavily upon the membership of the Academy and the Heart Association for advice not only in the planning of which I have spoken, but also for the Advisory Committee which now guides our policies, the visiting and advisory staffs at West Haverstraw, and in other ways. Briefly, these objectives are:

1. To provide through the development of cardiac clinics (meeting the standards of the American Heart Association as adapted from those of the New York Heart Association) foci for the diagnosis of rheumatic heart disease in children and for the graduate instruction of physicians in the same;

2. To provide, through the cardiac service at the State Reconstruction Home, as ideal care as possible for children and young adults up to the age of 21 years, who reside within a reasonable distance of that institution; and otherwise, to aid communities in the organization of all of their existing agencies and facilities which might serve this objective;

3. To pursue, in coöperation with the State Medical Society, and other qualified medical groups, an active graduate medical educational program directed toward more exact diagnosis and correspondingly better handling of heart disease in children;

4. To pursue such opportunities as may present themselves for study of the epidemiology and public health aspects of rheumatic disease.

It is relevant to point out, in connection with the second objective, i.e., the provision of care, that it has never been clearly shown whether or not the specific benefits of convalescent hospital care might also be obtained by other and possibly less costly means.^{13, 16} Our plan, therefore, purposes, if possible, to study the practicability and value, both from a scientific and administrative point of view, of prolonged convalescent hospital care and rehabilitation of children who present a reasonably favorable prognosis, in comparison to home care for a similar group of children who, however, will receive the benefits of qualified medical and public health nursing supervision, social supervision including improved housing and other necessary environmental adjustments, and all other benefits of which reasonable community organization is capable.

I should like, if I may, to return to the program as it relates to New York City, in which you are more particularly interested, and to which this discussion is directed primarily. Here we are confronted by a problem in which over a dozen organizations, voluntary agencies, and governmental departments, have developed a high degree of interest and, some of them, considerable activity. Obviously a common meeting ground is required, a point where the facilities, ideas, plans and problems of these agencies, all administratively independent, may be cleared and from which they may proceed to function in an efficient manner.

There are two major administrative procedures that might be applied: One, direct supervision or, as it is sometimes called, vertical administration; the other, collaboration of agencies along lines of more or less horizontal administration. Both require an administrative unit but in the former it is regulatory; in the latter, persuasive in its functions.

I wish to venture the view that for the problem at hand neither is suited. In this country, we mistrust bureaucracy. It is perhaps justifiable in an emergency where time is of major importance but ordinarily we consider it dangerous and un-American. We believe that many qualified minds form better judgments than a single mind and we are disinclined to regiment easily. On the other hand, individualism and autonomy can most certainly be carried to a fault and unless care is taken we find that such administrative autonomy tends to become the objective and attention is diverted from the fulfillment of the original purpose.

We all are acquainted with voluntary service organizations of one kind or another, some of which work splendidly with discipline and dignity, others of which fail completely. It is of the utmost importance that we find what the difference is between these and be correspondingly guided. The answer seems simple. Is it not in sincerity of purpose? If we are deeply concerned with a problem, will not small interests tend to disappear and be replaced by voluntary submission to a reasonable and sincere administrative direction? The rational approach seems to lie between the undesirable extremes of regulation, which in this case cannot be considered, and the impotence of the so-called coöperative program which so often dies with its lips still serving. In order to describe this rational approach, I have chosen the term *coagency* because, to me, it seems to connote that degree of positiveness in coöperation upon which success may well depend.

Let us, by way of illustration, inspect a few aspects of our problem and see how dependent it necessarily must be upon a functioning coagency.

First, there is the question of case finding. Here in New York City perhaps this will not present the developmental difficulties that it might in a city with less well-organized clinic facilities and provision for school medical inspection. Both are major sources. In 1934, according to Swift,² approximately 1800 children were discharged from New York City hospitals with varying degrees of rheumatic carditis. There is no central registry of these as in London and at present their further care is largely a matter of the affiliations of the hospital from which they were discharged, and the interest of the medical social services. Well over 5,000 cases of rheumatic heart disease are treated annually in the fifty-six affiliated clinics of the New York Heart Association.² Records

of these are available to the Association, but there is no mechanism for clearing them with the records of many of the hospital discharges, nor of cases detected in other ways, such as through school medical inspection, and more particularly the patients carefully diagnosed and registered by the City Department of Health through its excellent new Cardiac Classification Service.

And what if these patients, as well as those found in private practice or through other channels, were all cleared through a central point? Could the diagnosis be considered as sufficiently accurate for a registry upon which service and studies would both depend? The experiences of Paul¹⁷ and of Rutstein¹⁸ suggest that they cannot be so considered. For uniform standards of diagnosis, the skill of specially qualified diagnosticians appears necessary. To be sure, most creditable steps already have been made in this direction here in New York City, but means should be found for their further extension if the total problem is to be clarified.

In considering other possible methods of case finding, one cannot escape the question as to whether or not better knowledge of the epidemiology of the disease may lead, as it is doing in tuberculosis, directly to families or situations where the mass of cases may be found. The studies of Paul¹⁹ and Gauld and his associates²⁰ strongly indicate this as a possibility. If it proves true, new mechanisms must be developed which will probably be a major concern of the health department.

Second, having found the patients, what is to be done? A certain proportion will need continued convalescent hospital care and gradual rehabilitation. All will require regular medical supervision for a period of years at a clinic or by their own physician. A large majority will require careful study of their home and social-environmental problems.²¹ Many will require adjustments.

There are still far too few beds for the convalescent care of children with rheumatic heart disease to approach the estimated need in this city,² despite the recent expansion of facilities at St. Francis Sanatorium at Roslyn, Long Island, and the opening of the ninety-six bed service by the State Department of Health at its Reconstruction Home at West Haverstraw. Admission of patients from medically indigent families to these and the other available services follows different patterns varying from simple clearance through a medical research clinic into its endowed convalescent wards, to care at city expense administered by the Depart-

ment of Social Welfare, or as in the case of the New York State Reconstruction Home, care at shared City and State expense through the agency of the Domestic Relations Court and the State Department of Health.

The problem of medical supervision through clinics and private physicians is closely related to that of the follow-up observation of patients discharged from the several specialized convalescent hospitals. All of these institutions are investigative in their point of view, and are certainly entitled to any reasonable data that they may require. Yet, attempts to obtain these data must be carefully protected from falling on innumerable obstacles. It is a problem with which clinic social workers, school medical services, public health and visiting nurses, as well as physicians, will find themselves concerned.

Likewise, the problems of meeting the social-environmental and educational needs of these children cross many administrative lines and enter into the jurisdictions of several departments of government as well as being the concern of voluntary agencies.

Third, there is the question of administration. At the Federal level, the chief agency is the Children's Bureau, which, through its administration of Social Security funds for Crippled Children's Services, is in a strong position to encourage and influence the standards of State programs and of related medical care. The actual determination of policy, however, resides with the States, but New York State, under the law, has no health jurisdiction in New York City, save for its general responsibility for the expenditure of Federal Funds. I look, therefore, to the time when the City Department of Health will be in a position to incorporate certain phases of the program in the activities of its crippled children's service.

It is probably unnecessary to go further to picture the amazing amount of interlacing and the complexity of the administrative problem that faces us. Disease has often been said to have no respect for boundaries or political lines. I may add that neither does it respect man's ideas of administrative orderliness. If we are to succeed, we, as a group of agencies, must be willing to cross the preconceived lines of our several organizations where and when indicated by sound judgment. By so doing alone, can we hope to accomplish our objective with the greatest economy of facilities, manpower and expense.

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STUDIES ON HEADACHE: THE MECHANISMS AND SIGNIFICANCE OF THE HEADACHE ASSOCIATED WITH BRAIN TUMOR*

E. CHARLES KUNKLE, BRONSON S. RAY and HAROLD G. WOLFF

HEADACHE of patients with brain tumor has been considered to be of limited clinical interest. The mechanism of its production has been incompletely understood and its value in localization of the lesion has been minimized. This restriction of interest in the clinical importance of the headache has at least two explanations: first, the location of the pain has seemed to bear little relation to that of the tumor;^{1,2,3} and second, tumor headache has been held to be a manifestation of generalized increase in intracranial pressure, and therefore of little value in localization. The observations which have been made regarding the association of headache in certain sites with specific tumor types or locations are few.^{4,5,6,7,8,9,10,11} In these, the emphasis is placed upon the occipital headache characteristic of cerebellar tumors and the frontal reference of pain when such lesions produce internal hydrocephalus. The current generally accepted view of the localizing value of brain tumor headache is summarized in two sentences from a text-book of medicine written seventy-three years ago: "Pain in the head [in patients with brain tumor] is frequently limited to a circumscribed space, but the locality may not correspond to the site of the tumor. The pain, however, is generally on the side of the head corresponding to the situation of the tumor and is referred to the occiput if the tumor be situated in or upon the cerebellum."¹²

THE PROBLEM

The purposes of this study were: (1) to define the quality and intensity of brain tumor headache; (2) to ascertain in how many cases the occurrence and location of the headache could be explained and to outline the common mechanisms of brain tumor headache; and (3) to

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define when headache might be expected to have value in diagnosis and localization of brain tumor.

PATIENT MATERIAL

Seventy-two patients with primary brain tumor were selected. Only those patients who made adequate descriptions of symptoms were studied. In all, the location, size and type of tumor were established at operation or autopsy. The tumors were grouped as follow:

| | | |
|--|-------|-------|
| Supratentorial tumors: | | |
| Meningioma | | 15 |
| Glioma | | 22 |
| Glioblastoma multiforme | | 13 |
| Oligodendroglioma | | 3 |
| Astrocytoma | | 2 |
| Angiosarcoma | | 2 |
| Ganglioneuroma | | 1 |
| Neuroblastoma | | 1 |
| 3rd ventricle tumors | | 2 |
| Hypophysial adenoma | | 8 |
| Craniopharyngioma | | 7 |
| | | <hr/> |
| | | 54 |
| Infratentorial tumors: | | |
| Cerebellopontile angle tumors | | 7 |
| Meningioma | | 1 |
| Trigeminal "neuroma" | | 1 |
| Acoustic "neuroma" | | 5 |
| Cerebellar and fourth ventricle tumors | | 11 |
| Astrocytoma | | 5 |
| Hemangioblastoma | | 2 |
| Angiofibroma | | 1 |
| Medulloblastoma | | 1 |
| Meningeal sarcoma | | 1 |
| Glioblastoma multiforme | | 1 |
| | | <hr/> |
| | | 18 |

Headache, either continuous or more frequently intermittent, was present in sixty-five or 9/10, and increased intracranial pressure, in forty-nine or about 7/10 of the patients. The evidence for increased pressure included one or more of the following criteria: papilledema, accentuated convolutional markings on roentgenogram of the skull, ventricular dilatation on ventriculogram, definite manifestations of pressure increase when the ventricles were tapped or the bone flap turned down, and elevated cerebrospinal fluid pressure on lumbar tap.

I. THE QUALITY AND INTENSITY OF BRAIN TUMOR HEADACHE

The headache was of a deep, aching, steady, dull nature. It was not rhythmic and seldom throbbing. It was usually intermittent, but in one tenth of the patients it was continuous. The headache was sometimes

severe, but rarely was it as intense as that of migraine or the headache associated with ruptured cerebral aneurysm, meningitis, or certain febrile illnesses or that induced by certain drugs. It was usually relieved by acetylsalicylic acid, or cold packs applied to the scalp, both indications of its moderate intensity. It rarely interfered with sleep. It was aggravated by coughing, or straining at stool and sometimes it was worse in the erect than in the recumbent position. It was commonly aggravated also by the onset of a minor infection. If there were any variation in intensity during the twenty-four cycle, it was worse in the early morning.

Even when the tumor directly compressed or extensively stretched cranial nerves containing pain afferents, the pain was not equal in intensity to that of *tic douloureux*, and indeed was often mild or absent.^{4,6,8,13}

Unless the pain were severe, nausea with tumor headache was slight. Vomiting occurred with displacement or compression of the medulla¹⁴ and was sometimes "projectile," perhaps because it was unexpected when unaccompanied by nausea. The headache when occipital or suboccipital was sometimes associated with "stiffness" or aching of the muscles of the neck and tilting of the head toward the side of the tumor.

II. THE MECHANISMS OF BRAIN TUMOR HEADACHE

Two sets of recent observations on headache mechanisms directly introduce the present study. First of all, data obtained during the operative exposure of intracranial contents have identified those structures which are pain sensitive to mechanical stimulation, and the sites of the headache thus induced.^{15, 16, 17, 18} These structures are, in brief, the great venous sinuses and their tributaries from the surface of the brain, the dural arteries, the internal carotid arteries, the cerebral arteries at the base, the basilar and vertebral arteries, the other arteries near their sites of origin from the basilar and vertebral trunks, parts of the dura at the base, and the intracranial portions of the trigeminal, glossopharyngeal, vagus and upper cervical nerves. It was noted, furthermore, that stimulation of the pain sensitive structures on or above the superior surface of the tentorium cerebelli resulted in pain transmitted by the fifth nerve and located in regions on the anterior half of the head.

Stimulation of the pain sensitive intracranial structures on or below the inferior surface of the tentorium cerebelli resulted in pain over the posterior half of the head, the pain pathways being chiefly in the ninth

HEADACHE SITES AND INTRACRANIAL STRUCTURES INVOLVED

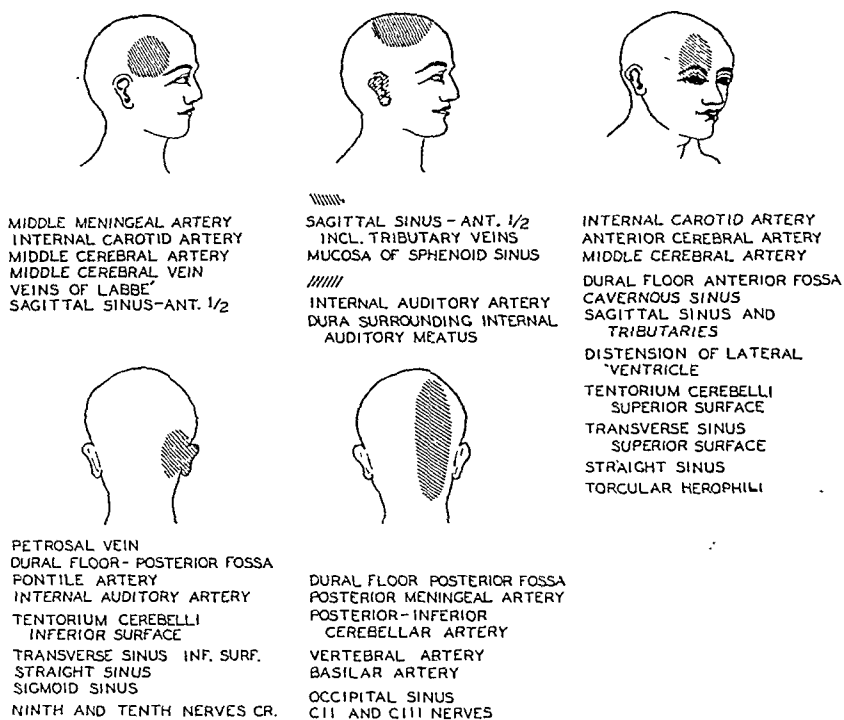


Fig. 1—Summary of intracranial pain sensitive structures which may be the sources of headache in the various main divisions of the head. Chart is based upon data obtained at operative exposure of intracranial contents.

and tenth cranial nerves and the upper three cervical nerves.¹⁸

These facts of pain reference are illustrated on a chart (Fig. 1) representing the sites of intracranial disease which may account for headache in the various main divisions of the surface of the head.* The chart demonstrates the difficulties inherent in any attempt to use headache as a localizing sign of intracranial disease, since lesions of remotely separated structures within the skull may cause headache in identical areas.

Organization of the data available from these studies has indicated six basic mechanisms of headache, involving distortion or inflammation of intracranial pain sensitive structures.¹⁸

1. Traction on the large venous sinuses or their tributaries from the surface of the brain.
2. Traction on the middle meningeal artery.

* Eye and paranasal sinus diseases have been eliminated from consideration here. The role of these factors in headache is now being studied.

3. Traction on the large arteries at the base of the brain.
4. Direct pressure upon the cranial and upper cervical nerves which carry pain fibers.
5. Dilatation of intracranial arteries.
6. Inflammation in or about any of the intracranial pain sensitive structures.

It has been suggested that the first four of these six mechanisms may play a part in the headache associated with brain tumor.¹⁸

A second fact important to an understanding of brain tumor headache is that increased intracranial pressure is not essential to its production.¹⁹ Thus, elevation of the intracranial pressure in normal human subjects to levels as high as 510 mm. of saline by the intrathecal injection of normal saline consistently failed to cause headache. Evidence even more compelling that increased intracranial pressure and tumor headache are not closely related was obtained in the study of a man with a left parietal oligodendroglioma in whom bifrontal headache had been present intermittently for two months but happened to be absent at the time the following experiment was performed.¹⁹ By drainage of cerebrospinal fluid with the patient horizontal, moderate headache, chiefly left frontal, was induced. The headache was then relieved at once by restoration of fluid and elevation of pressure to its initial level, and furthermore could not be produced by pressure elevation to a high level, 550 mm. of saline. (See also Northfield¹⁰ and Pickering.²⁰)

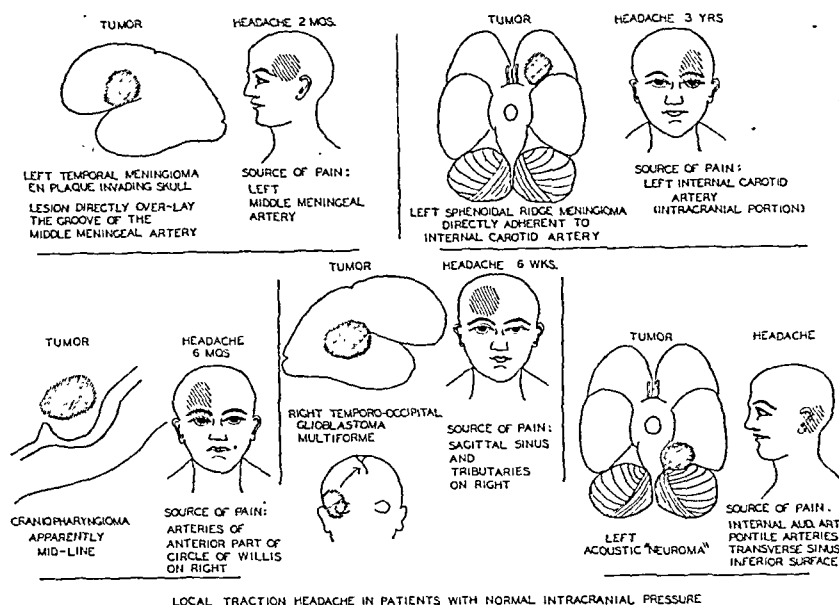
1. *Tumor Headache and Increased Intracranial Pressure not Essentially Related:*

In this series of seventy-two patients, the symptom headache occurred almost as commonly in those patients (19 of 23, or about 8/10) without increased intracranial pressure as it did in those (46 of 49, or about 9/10) with increased pressure. Moreover, of the seven patients (about 1/10 of all cases) who were headache-free, three had increased intracranial pressure.

These data demonstrate that increased pressure per se is neither an essential nor a major factor in tumor headache.

2. *Tumor Headache in Patients with Normal Intracranial Pressure—The Mechanism of Local Traction:*

Of the twenty-three patients with normal intracranial pressure, nineteen had headache as a symptom. In all but three patients with hypophysial adenoma, the existence and location of the headache could be

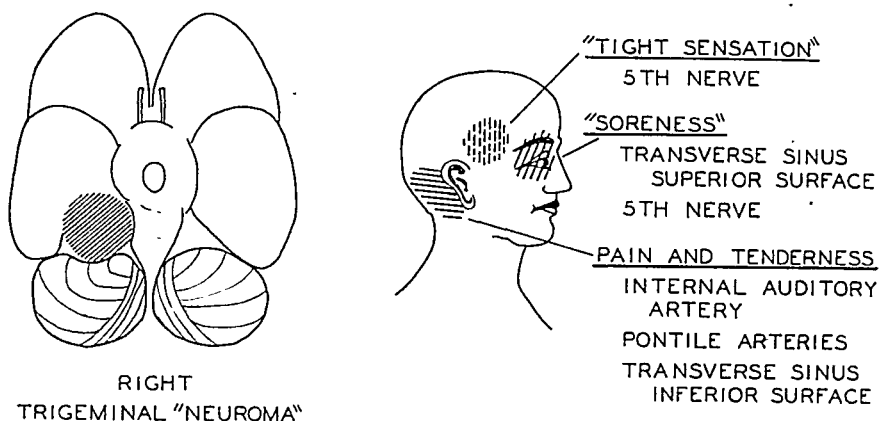


LOCAL TRACTION HEADACHE IN PATIENTS WITH NORMAL INTRACRANIAL PRESSURE

Fig. 2—Five examples of patients with tumor headache produced by local traction. Intracranial pressure was normal in all. The structures which were the probable sources of the pain are listed in each case.

explained by traction upon or distortion of directly neighboring pain sensitive structures, and in some at operation the headache was thus reproduced. These adjacent structures were: (1) for the four supratentorial meningiomas—the superior sagittal sinus and its tributaries, the middle meningeal artery and the large arteries at the base; (2) for the one glioma—the superior sagittal sinus and its tributaries; (3) for the three craniopharyngiomas—the large arteries at the base; (4) for the four hypophysial adenomas—the large arteries at the base and in one patient the lining of the sphenoid sinus; and (5) for the four cerebellopontile angle tumors—the internal auditory artery, the pontile arteries, the dura about the internal auditory meatus, and the transverse sinus. In Fig. 2 are shown examples of this group.

Another example of the headache produced by local traction may be cited (Fig. 3). A thirty-seven year old male with a trigeminal "neuroma" in the right cerebellopontile angle and no evidence of increased intracranial pressure had had for four months three separate kinds of head discomfort. These, with the sites of origin of the symptoms, were: (1) right temporal "tightness"—fifth cranial nerve; (2) "soreness" in the



HEADACHE WITH AN ANGLE TUMOR

Fig. 3—Demonstration of local traction headache mechanisms in an adult male with three separate types of head discomfort, due to a trigeminal "neuroma" in the right cerebellopontile angle. The intracranial pressure was normal.

right eyeball, superior surface of the right transverse sinus and fifth cranial nerve; (3) pain and tenderness in the right postauricular area; right internal auditory and pontile arteries and inferior surface of the transverse sinus.

This mechanism of tumor headache may be termed local traction. While independent of increase in intracranial pressure, it may well be augmented by generalized displacement of the brain associated with cerebrospinal fluid pressure rise.

The three patients with hypophysial adenoma in whom local traction did not entirely account for the headache had pain in the occiput or subocciput in addition to frontotemporal headache. The pain in the back of the head in these three of the seven patients with hypophysial adenoma is unexplained.

3. Tumor Headache in Patients with Increased Intracranial Pressure *—The Mechanisms of Local and Distant Traction:*

In less than one-half (18) of those patients (46) with headache and increased intracranial pressure could the locations of the headache be explained or the pain induced by local traction. Most of the remaining half of the patients had posterior head pain in association with supratentorial tumors and frontal headache in association with infratentorial

tumors. The following analysis of the group illuminates this seeming paradox.

A. DISTANT TRACTION THROUGH EXTENSIVE DISPLACEMENT OF THE BRAIN:

Slightly less than one-half (14 of 32) of the patients with supratentorial tumor with headache had pain in the posterior half of the head—occipital, suboccipital or postauricular areas. In seven patients this pain was bilateral. In the seven in whom it was unilateral it was homolateral to the tumor in all but one. In each instance pain was also present in one or several other head regions.

Headache so located in these patients could not be explained by local traction, for there is no evidence that any supratentorial structure can be the direct source of posterior head pain. Pressure downward upon the tentorium cerebelli from above has been shown experimentally to cause only fronto-orbital pain,¹⁸ probably by traction upon the upper surfaces of the transverse sinuses. Such a mechanism, therefore, cannot be relevant to posterior head pain. It has been recognized, however, that when supratentorial lesions are large enough to cause generalized increase in pressure, there is often a widespread shift in the brain causing distortion of supra- and infratentorial structures. Thus, traction or pressure upon the transverse and occipital sinuses, the basilar and vertebral arteries, the ninth and tenth cranial and upper cervical nerves is probably a common occurrence. However, with supratentorial tumor the extent of such distortion in the posterior fossa is much less and the establishment of a "cerebellar pressure cone" is less likely than in patients with infratentorial tumor.

Herniation of the hippocampal gyri through the incisura tentorii may also be responsible for posterior head pain from supratentorial tumors. In a recent review of autopsied cases of supratentorial neoplasms such a complication was found in about 8/10 of the series.²¹ The distortion produced by this "temporal pressure cone" has been shown to affect not only the hippocampal gyri but also the adjacent brain stem, and presumably the basilar artery and its branches. This mechanism must be considered to be of minor importance as regards the present problem, for in the autopsied series reported, posterior head pain was no more common in the patients with such herniation than in those without it.

In brief, posterior head pain in patients with supratentorial tumor appears to depend upon expansion of the mass to such an extent that

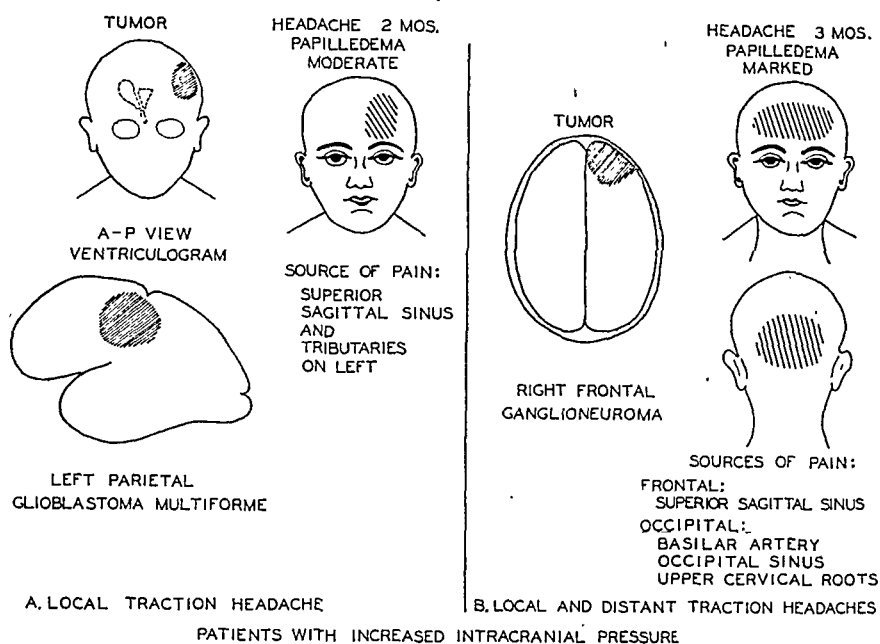
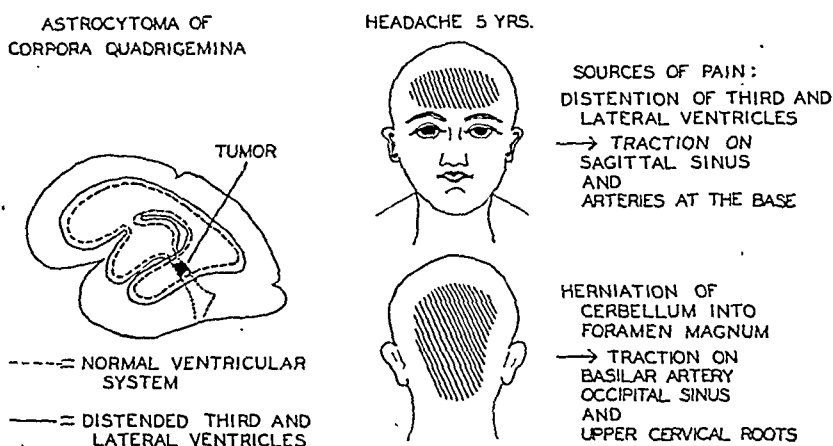


Fig. 4—Local and distant traction mechanisms in tumor headache contrasted in two patients with increased intracranial pressure. In A the headache was due to local traction alone; in B the frontal headache was due to local traction, the occipital headache to distant traction.

coincident with generalized rise in intracranial pressure, traction is produced upon pain sensitive structures in the distant posterior fossa, by displacement of the whole brain. In contrast to local traction this may be conveniently termed distant traction and may be considered as a second mechanism of brain tumor headache. It is evident that in extensive shift of the brain, traction effected at a distance from the tumor may involve structures on the same side as the tumor or both sides. The data indicate that both situations are common.

Two cases of supratentorial tumor with increased pressure are illustrated in Fig. 4A and B. In A, a patient with a left parietal glioblastoma multiforme and moderate papilledema, the left frontal headache was due to traction locally by the mass upon the superior sagittal sinus and its tributaries on the left. The ventriculogram is reproduced in outline to emphasize the type of distortion which was present. In B, a patient with a right frontal ganglioneuroma and advanced papilledema, the frontal headache was similar in its mechanism to that of A. The occipital headache represented distant traction upon structures in the posterior fossa, secondary to widespread displacement of the brain.



DISTANT TRACTION VIA INTERNAL HYDROCEPHALUS AND CEREBELLAR "PRESSURE CONE"

Fig. 5—Demonstration of distant traction headache produced by a small astrocytoma in the roof of the aqueduct. The frontal headache was due to internal hydrocephalus, the occipital headache to distortion of posterior fossa structures by wedging of the cerebellum into the foramen magnum.

B. DISTANT TRACTION THROUGH INTERNAL HYDROCEPHALUS:

Frontal headache was a symptom in two-thirds (10 of 14) of the patients with infratentorial tumor and increased intracranial pressure, all of whom had headache. This fact likewise required explanation in terms other than local traction by the tumor. Analysis revealed that 9 of the 10 with frontal headache, comprising 2 angle tumors and 7 cerebellar or fourth ventricle tumors, were complicated by block to the cerebrospinal fluid outflow at the aqueduct or the fourth ventricle and had internal hydrocephalus with increase in intracranial pressure. The frontal headache was bilateral in all but one patient.

The association of internal hydrocephalus with frontal headache in patients with infratentorial tumor has been noted by others.^{5, 8} Direct evidence that the hydrocephalus is causally related to the headache has been provided by the demonstration that distention of one lateral ventricle with a balloon at operation induces homolateral frontal headache¹⁸ by traction upon the veins over the convexity of the brain anchoring it to the superior sagittal sinus. Experimental distention of the third ventricle has been found to cause diffuse headache arising from traction upon the many large vessels at the base. There is further evidence that

significant distortion of adjacent structure at the base is produced by enlargement of the third ventricle in internal hydrocephalus, for in such patients a visual field defect indicative of chiasmal pressure has often been found.²² The usual bilaterality of the frontal headache in these patients may therefore be understood.

Hence, frontal headache of this kind is like the posterior head pain discussed in the previous section in that it is produced by traction at a distance from the tumor.

An example of a small tumor producing headache entirely by distant traction is outlined in Fig. 5. A sixteen year old male had intermittent bifrontal and bioccipital headache for five years. On admission moderate papilledema was noted. The ventriculograms showed advanced dilatation of the third and lateral ventricles. Exploration confirmed the presence of internal hydrocephalus. The foramina of Monroe were widely stretched, the largest diameter of the left opening measuring 2.5 cm. Moreover, as seen in a second exploration, the tonsils of the cerebellum were herniated in part into the foramen magnum. No tumor could be found, but autopsy revealed a small fibrillary astrocytoma of the corpora quadrigemina occluding the aqueduct of Sylvius. The frontal headache was due to distention of the lateral, and possibly the third, ventricles. The occipital headache was due to traction upon the basilar artery, the occipital sinus, the ninth and tenth cranial nerves and upper cervical roots by the wedging of the cerebellum down into the foramen magnum. The site of origin and the location of both frontal and occipital headaches were remote from the tumor itself.

C. TUMOR HEADACHE UNEXPLAINED BY LOCAL OR DISTANT TRACTION:

In two patients with increased intracranial pressure the headache could not clearly be related to these mechanisms. One, a twenty-four year old female, had a left temporal headache for five months. She had a right acoustic "neuroma," increased intracranial pressure and internal hydrocephalus.

The other, a forty-four year old female, had right occipital headache for six months. She had a left cerebellar hemangioblastoma, increased intracranial pressure and internal hydrocephalus.

Headache in this pattern, sparing the homolateral side but involving the contralateral side, appears bizarre. The direction and distribution of the stress and strain in these two cases is conjectural and the factors

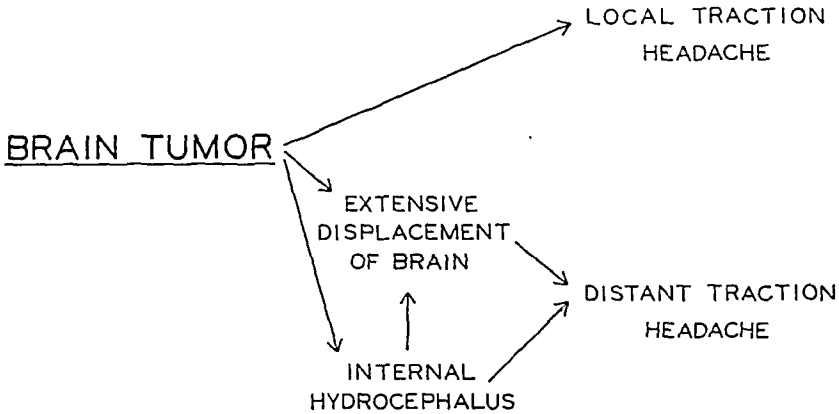
HEADACHE MECHANISMS IN BRAIN TUMOR

Fig. 6—Schematic outline summarizing common mechanisms of brain tumor headache.

which make them atypical are not apparent. There is no evidence, however, that mechanisms other than traction upon pain sensitive structures are involved.

Thus, in forty-four of the forty-six patients with headache and increased intracranial pressure the existence and location of the headache could be accounted for on the basis of the mechanisms thus far outlined. In many (18) local traction alone appeared to be responsible. In a few (4) traction at a distance alone was responsible, either through displacement of posterior fossa structures in patients with supratentorial tumors or through internal hydrocephalus in patients with infratentorial tumors, but, in the largest group (22) both local and distant traction were concerned. In 2 patients the headache could not be clearly explained by either mechanism.

It is to be emphasized that the association of increased intracranial pressure with headache due to distant traction does not justify the inference that increased intracranial pressure of itself causes headache. It indicates rather that the same factors which bring about distant traction, that is, extensive displacement of the brain directly by the tumor or indirectly by internal hydrocephalus, will also cause generalized elevation of intracranial pressure. (See Fig. 6.)

4. *Continuous vs. Intermittent Headache with Brain Tumor:*

As mentioned above, the headache of brain tumor is usually inter-

mittent. In this series continuous headache was noted in only seven cases or about a tenth of the patients (all with supratentorial tumor). Four of these had increased intracranial pressure. Local traction appeared to be the mechanism in all seven cases. The persistence of the headache in these cases is not surprising, for it is reasonable to expect local traction to be continuous, and in fact progressive, if the tumor growth is moderately rapid. There is no explanation of the intermittency of the headache that will apply to all the remaining large group of patients. In some, intermittent block to cerebrospinal fluid outflow either because of varying states of brain hydration or by movable tumors in the 4th or 3rd ventricles appears to have been responsible. In others the increase in intracranial venous pressure with straining and coughing might have been the basis for occasional headache.

5. *Patients with Brain Tumor without Headache:*

Seven patients, or about a tenth of the entire series, had no headache in association with their lesions. The tumors represented were all supratentorial; in three of the seven increased intracranial pressure was present.

Associated with increased intracranial pressure and without headaches were:

| <i>Tumor Type</i> | <i>Site</i> |
|-------------------------|----------------------------|
| Meningioma | left parasagittal parietal |
| Glioblastoma multiforme | right frontocallosal |
| Glioblastoma multiforme | left frontal (subcortical) |

Associated with normal intracranial pressure and without headaches were:

| <i>Tumor Type</i> | <i>Site</i> |
|-------------------|---|
| Meningioma | right frontotemporal (invading the skull) |
| Oligodendroglioma | left frontotemporal |
| Oligodendroglioma | right temporoparietal |
| Craniopharyngioma | suprasellar (sella and dorsum destroyed) |

Review of these patients disclosed that the only characteristic common to all was a supratentorial location of the tumor.

The absence of headache in patients with brain tumor may be related to the slow growth of the neoplasm. Thus five of the above seven patients had lesions which are notably slow in expanding, i.e., meningioma, craniopharyngioma and oligodendroglioma. Moreover, in one of the two patients who were headache-free with glioblastoma multiforme, ordinarily a rapidly growing neoplasm, the clinical course indicated unusually slow growth of the tumor. When expansion of the tumor mass is slow, mechanical adaptation of adjacent structures may be sufficient to

prevent pain production. This may represent the return of distorted pain endings to normal contour even though gross distortion of the tissues in which the pain endings are embedded persists. When the pace of growth is fast, such adaptation may be inadequate.^{6, 13}

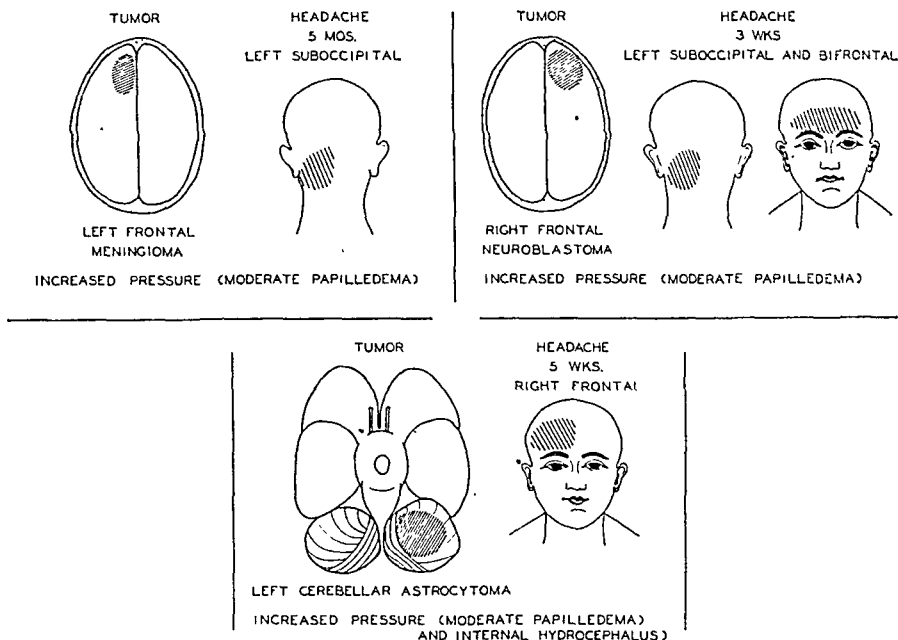
It may be noted that in contrast to tumors above the tentorium, posterior fossa tumors, whatever their rate of growth, rarely fail to cause headache, undoubtedly because many of these lesions cause internal hydrocephalus.^{5, 8} In consideration of headache the speed of growth of the posterior fossa tumor is less significant since it bears no direct relation to the completeness of occlusion of the third or the fourth ventricle. A block once induced results in a relatively sudden displacement of the brain and stimulation of local and distant pain sensitive structures.

Serious sensorial defects produced by the tumor, particularly with frontal lobe lesions, may be a second cause for absence of headache. For example, in the second of the two patients with glioblastoma multiforme without headache, listed in the table above, the tumor was in the right frontocallosoal region and apathy and confusion were early and dramatic symptoms. Under such circumstances, gross defects in reaction to pain may veil or completely mask headache.

Invasion of the skull by meningiomas may be still a third factor in preventing or delaying headache. The bone of the skull is insensitive and extension in this direction may take the place of greater intracranial expansion toward pain sensitive structures.

6. Consideration of Other Suggested Mechanisms.

In these formulations distortion of pain sensitive structures has been described as the chief basis for brain tumor headache. Factors other than traction have been suggested by others but not established as relevant mechanisms. Dilatation of intracranial veins and arteries, which occurs secondary to generalized increase in intracranial pressure, may conceivably be a cause of headache.^{10, 18} Such vasodilatation must, however, be of minor importance as a cause of headache in patients with tumor since it has been shown in this discussion that increased intracranial pressure is not essential to the headache, and the pain in these patients is usually localized rather than diffusely distributed as it should be if generalized dilatation of intracranial vessels were the cause. Stretch of the dura mater over the convexities of the cerebrum and cerebellum by the rise in intracranial pressure is also probably not a significant mechanism, because the dura and pia in these areas are insensitive.



TUMOR HEADACHE AS A MISLEADING SIGN IN PATIENTS WITH INCREASED INTRACRANIAL PRESSURE

Fig. 7—Demonstration of headache as a grossly misleading sign of the location of brain tumor when it is due to distant traction. Extensive displacement of the brain and increased intracranial pressure were present in all three patients.

III. HEADACHE IN THE LOCALIZATION OF BRAIN TUMOR

A. LIMITATIONS OF HEADACHE AS A LOCALIZING SIGN:

1. *Headache in Association with Increased Intracranial Pressure of Limited Localizing Value:*

In the preceding section it was noted that headache in patients with normal intracranial pressure could, with rare exceptions, be explained entirely in terms of local traction. Of patients with increased intracranial pressure in only eighteen of forty-six, or about 4/10, was local traction solely responsible; in the remaining twenty-six distant traction was an accessory or the chief mechanism.

When distant traction is involved the problem of localization of the tumor is complicated, for with this mechanism distortion of bilateral pain sensitive structures is common, and the site of the expanding mass is often concealed. It is evident, therefore, that in the presence of increased intracranial pressure, which in patients with brain tumor is

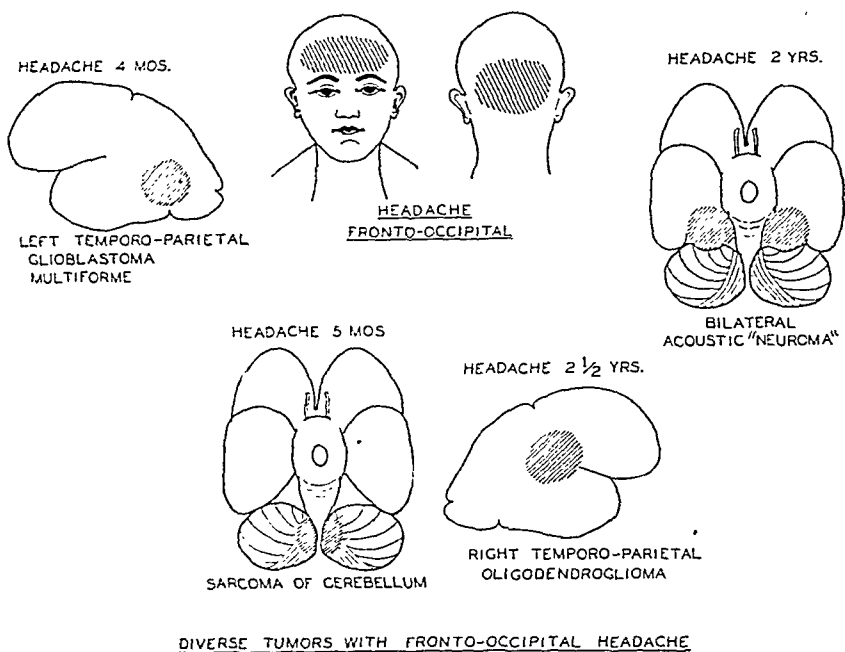


Fig. 8—Demonstration of fronto-occipital headache occurring with tumors of widely varying types and locations and therefore of no localizing value. Extensive displacement of the brain and increased intracranial pressure were present in all.

presumptive evidence of extensive displacement of the brain, the localizing value of tumor headache becomes reduced. Examples of patients with headache as a misleading sign when secondary to distant traction are shown in Fig. 7.

2. *Fronto-occipital Headache of No Localizing Value:*

The combination of frontal and occipital headache was noted in one-quarter of all the patients with headache. The group with fronto-occipital headache included patients with meningioma, cerebral glioma, third ventricle cyst, hypophysial adenoma, cerebellopontile angle and cerebellar and fourth ventricle tumors. Except for the two instances of hypophysial adenomas, all were accompanied by increased intracranial pressure. Internal hydrocephalus was present with only one of the supratentorial tumors, the 3rd ventricle cyst, but was present with all five infratentorial tumors.

The data indicated that fronto-occipital headache occurred almost as frequently with supratentorial tumors as with those below the ten-

torium. Moreover, they showed conclusively that the fronto-occipital headache combination cannot be considered diagnostic of internal hydrocephalus in patients with brain tumor. It is of additional interest that except for the hypophysial adenomas all of the patients with headache of this pattern had increased intracranial pressure.

Four typical instances of brain tumor of contrasting types and location, all presenting fronto-occipital headache, are outlined in Fig. 8.

3. *Headache Over the Vertex—Infrequent and of Little Localizing Value:*

Headache over the vertex was noted infrequently in this series. In only three patients was the headache in the vertex alone; these were a mid-line olfactory groove meningioma, a craniopharyngioma and an eosinophilic hypophysial adenoma. In the first two the intracranial pressure was elevated. In two other patients headache was vertical in part but not predominantly; the tumors found were a parasagittal parietal meningioma and a mid-line cerebellar astrocytoma, both with increased pressure.

4. *Headache from Mid-line Tumors Not Always Bilateral:*

Twenty-three mid-line tumors with headache were included in this series. In seventeen patients the headache was symmetrically bilateral, eleven having increased intracranial pressure. In six the headache was entirely or predominantly unilateral; none of these had increased intracranial pressure.

Local traction apparently was the mechanism for the headache when it was unilateral. The inequality of the distortion produced may have been due to unrecognized asymmetrical expansion of the growing tumor. Whatever the explanation, it is clear that unilateral headache may occur with mid-line tumors.

B. THE ASSETS OF HEADACHE AS A LOCALIZING SIGN:

The limitations of headache having thus been considered, its value may now be appraised.

1. *Headache Near or Overlying the Tumor:*

Headache to be of service as a localizing sign of brain tumor must be interpreted in terms of the headache mechanisms and principles of pain reference just outlined. Only when tumor headache is caused solely by local traction is it of direct value in localization. Even then the headache may not overlie the tumor, for in about 4/10 of the patients with

headache due only to local traction the pain was not immediately over the tumor. In the following analysis certain tumors located at the base and anteriorly were not included since obviously they could not produce headache near to or directly overlying the tumor, other than in the nasopharynx. These lesions were the craniopharyngiomas, hypophysial adenomas, a suprasellar meningioma, and a third ventricle cyst. The evidence in summary, based on the remaining 22 patients with local traction headache, was as follows:

| | <i>Headache was near to or overlying the Tumor</i> |
|---|--|
| Supratentorial Tumors | |
| Meningioma | 3 of 6 |
| Glioma | 4 of 9 |
| Infratentorial Tumors | |
| Cerebellopontile angle tumors | 4 of 4 |
| Cerebellar and 4th ventricle tumors | 2 of 3 |
| | <hr/> 13 of 22 |

When the analysis was broadened to include all the patients (again excluding the tumors at the base) headache was found to overlie the tumor in only nineteen of fifty-one, or about one-third.

2. Headache as First Symptom of Brain Tumor:

With the exception of the cerebellopontile angle tumors, the presence of most of the posterior fossa tumors first was made manifest by headache. The tumors above the tentorium, on the other hand, were more likely first to cause other symptoms, as visual disturbances, paresthesias, convulsions, sensorial and personality changes. Other authors have reported similar observations.^{3, 6, 10} Northfield's figures¹⁰ based upon a series of 100 cases are presented in brackets for comparison with the data of this New York Hospital series. Headache as first symptom of brain tumor:

| In 54 cases of supratentorial tumor | | Northfield ¹⁰ |
|---|-----------------------------------|--------------------------|
| Meningioma | 5 of 15 | [36 per cent] |
| Glioma | 11 of 22 | [36 per cent] |
| 3rd ventricle tumors | 1 of 2 | |
| Hypophysial adenoma | 1 of 8 | |
| Craniopharyngioma | 2 of 7 | |
| | <hr/> 20 of 54 or about one-third | |
| In 18 cases of infratentorial tumor | | |
| Cerebellopontile angle tumors | 1 of 7 | [0] |
| Cerebellar and 4th ventricle tumors | 9 of 11 | [83 per cent] |
| | <hr/> 10 of 18 | |

The usual occurrence of headache as first symptom in patients with cerebellar or fourth ventricle tumors is related to the fact that internal

hydrocephalus can easily result from such lesions. Angle tumors, however, are less frequently associated with internal hydrocephalus in the early stages and are directly adjacent to the several cranial nerves which traverse the angle region, potential sources of such symptoms as facial paresthesias, deafness, tinnitus, or weakness of face or jaw. Whether or not supratentorial tumors cause focal symptoms or signs before headache appears depends upon the region of the brain involved.

3. *The Significance of Headache in the Back of the Head and Neck with Brain Tumor:*

Pain in the back of the head—occipital, or postauricular or suboccipital areas—was present alone or in part in one-half of the patients.* As described in a preceding section, such pain was present in seventeen of the forty-seven patients with supratentorial tumor with headache. In each of these, headache was present also in one or several other areas on the anterior half of the head. Except for the patients with hypophysial adenoma, headache in all was accompanied by increased intracranial pressure.

In contrast, pain in the back of the head was present in almost all of the patients with infratentorial tumor. Of the eighteen patients sixteen or almost 9/10 had posterior headache. The two without such headache had respectively an acoustic "neuroma" and a cerebellar astrocytoma, both accompanied by increased intracranial pressure.

It seems generally true, therefore, that occipital, suboccipital or postauricular pain did not of itself identify a tumor as being above or below the tentorium. On the other hand, the evidence did indicate that when posterior headache was absent the tumor was rarely infratentorial.

4. *The Significance of Headache in the Front of the Head with Brain Tumor:*

Frontal headache with brain tumor in this series was even more common than was pain in the back of the head. In 6/10 of all patients with headache, frontal headache was present, alone or with headaches elsewhere. In contrast to pain in or near the occiput, frontal headache was noted somewhat more often in association with supratentorial tumors (32 of the 47 with headache or about 7/10) than with infratentorial tumors (10 of 18 or about one-half).

Pain solely frontal was noted in eleven of the forty-seven cases of supratentorial tumor with headache but in only two of the eighteen

* For the sake of brevity pain of this type will be referred to hereafter as posterior headache.

cases with infratentorial tumor or headache.

The predominance of frontal headache is not surprising in view of the diverse ways, direct and indirect, in which brain tumor may produce pain referred to the frontal areas. But from the data it may be inferred that although frontal headache was common in all types and locations of tumor, the pain when solely frontal was usually due to supratentorial tumor.

5. *The Significance of Unilateral Headache:*

It has been shown above that mid-line tumors may cause unilateral headache, probably because of asymmetrical expansion of the mass. Further data concerning the significance of unilateral headache were derived from an analysis of the forty-two remaining patients with headache and tumor not in the mid-line. The headache patterns were as follows:

| | |
|---|----|
| Headache homolateral to the tumor | 24 |
| Headache contralateral to the tumor | 5 |
| Headache symmetrically bilateral | 13 |

All five patients with headache contralateral to the tumor had increased intracranial pressure. In three of these five the contralaterality of the headache was the result of distant traction.

It is evident that headache chiefly on one side of the head was common in these patients, and that in most cases the headache was on the same side as the tumor (See also Pickering²⁰). Contralateral headache may have resulted from the presence of anatomical asymmetries in the brain or skull such as the size or position of the lateral or third ventricles, or the relative position of the cerebellum, brain stem and anchoring structures in the posterior fossa. In none of the patients with normal intracranial pressure was contralateral headache noted. The important inference from these considerations is that headache solely or chiefly unilateral is probably on the same side as the tumor when the intracranial pressure is normal.

C. VARIOUS TYPES OF TUMORS IN RELATION TO HEADACHE:

Among patients with craniopharyngiomas, headache as an initial symptom was rare and its location unpredictable. The hypophysial adenomas also rarely produced headache as an initial symptom, and the site of the headache presented nothing of specific or helpful value.

Among most of the patients with headache due to cerebellopontile angle tumors the headache was a leading clue in the localization of the

lesion, although headache did not occur as an early symptom. Headache solely in the postauricular area was almost specific, especially before gross displacement of the brain occurred.

Among patients with meningiomas (all but one being supratentorial), headache was a first symptom in one-third. In about one-half of the fourteen patients with headache the headache was predominantly unilateral and on the same side as the tumor, and in all but two of the fourteen cases the headache was due to local traction. It might be expected that situated as the meningiomas are, in contact with pain sensitive structures at the base and over the convexities, that headache as an initial symptom might occur in a higher proportion than the one-third indicated. It is probable, however, that the slow growth and bone invasion offset the effects of proximity to pain sensitive vascular structures.

Gliomas, despite their lack of direct contact with pain sensitive structures, presented headache as a first symptom in one-half of the patients when they occurred above the tentorium and even more frequently when they occurred below. Such tumors produced headaches as an early manifestation probably because of their speed of growth and the likelihood of their occluding the lateral, third, and fourth ventricles.

D. GENERALIZATION:

From these studies the following generalizations concerning brain tumor headache as an aid to localization seem justified.

1. Although the headache of brain tumor is often referred from a distant intracranial source, it approximately overlies the tumor in about one-third of all patients.

2. Brain tumor headache in the absence of papilledema is of great localizing value. In about two-thirds of such patients the headache immediately overlies or is near the tumor and in all when unilateral it is on the same side as the tumor.

3. Headache is almost always present with posterior fossa tumor.

4. Headache may be absent with any of the common types of supratentorial tumor.

5. The headache of posterior fossa tumor is almost always over the back of the head, although it may occur elsewhere as well.

6. Headache is usually the first symptom of posterior fossa tumor except with cerebellopontile angle tumors.

7. Headache is the first symptom of one-third of supratentorial tumors.

8. The headache of cerebellopontile angle tumors is frequently and sometimes solely postauricular.

9. Headache from supratentorial tumors is rarely in the back of the head unless associated with papilledema.

10. When supratentorial tumors cause headache in the back of the head, headache in the front of the head is usually also present.

11. When headache is both frontal and occipital it indicates extensive displacement of the brain and has little localizing value.

12. Brain tumor headache is commonly intermittent but when it is continuous its value in localization is greatly enhanced.

CONCLUSIONS

1. Brain tumor headache is produced by traction upon intracranial pain sensitive structures, chiefly the large arteries, veins and venous sinuses, and certain cranial nerves. There are two types of traction which operate singly or in combination: local traction by the tumor mass upon adjacent structures; and distant traction by extensive displacement of the brain, either directly by the tumor or indirectly by ventricular obstruction (internal hydrocephalus).

2. As an aid in the localization of brain tumor, the value of headache is limited by two facts: the headache may be remote from the site of its production, and the site of production of the headache may be remote from the tumor.

3. In spite of these limitations, when it is interpreted in terms of known principles of intracranial pain production and pain reference, the headache of brain tumor may aid significantly in the diagnosis and localization of the lesion.

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PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

FEBRUARY 5—*The New York Academy of Medicine*. Executive session — Reading of the minutes. ¶ Papers of the evening — *Scientific program in conjunction with the New York Tuberculosis and Health Association* — Recent developments in the treatment of pulmonary tuberculosis — a] Physiological considerations, Dickinson W. Richards, Jr., Associate Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University; b] Surgical treatment, Frank B. Berry, Assistant Clinical Professor of Surgery, College of Physicians and Surgeons, Columbia University. ¶ Report on election of Fellows. ¶ Report on election of trustee.

FEBRUARY 19—*The Harvey Society (in affiliation with The New York Academy of Medicine)*. The Fifth Harvey Lecture, "Marijuana," Roger Adams, Professor of Chemistry, University of Illinois.

MARCH 5—*The New York Academy of Medicine*. Executive session— a] Reading of the minutes; b] Report of Nominating Committee. ¶ Papers of the evening— *Headaches*— a] General considerations, Harold G. Wolff, Associate Professor of Medicine, Cornell University Medical College; b] Clinical varieties and their treatment, Bayard T. Horton, Associate Professor of Medicine, Mayo Foundation. ¶ Report on election of Fellows, Honorary Fellow and Corresponding Fellow.

MARCH 19—*The Harvey Society (in affiliation with The New York Academy of Medicine)*. The Sixth Harvey Lecture, "Physiologic Studies Pertaining to Aviation Medicine and Deep Sea Diving," Albert R. Behnke, Lieutenant Commander, Medical Corps, U. S. Navy, Instructor in charge of Department of Atmospheric Hygiene, Navy Yard.

SECTION MEETINGS

FEBRUARY 3—*Dermatology and Syphilology*. Presentation of cases—From the Diagnostic and Treatment Centers, Bureau of Social Hygiene of the New York City Department of Health; and Cooperative Clinics. ¶ Discussion. ¶ Executive session.

FEBRUARY 6—*Surgery*. Reading of the minutes. ¶ Papers of the evening— a] The method of measuring the electrical potential difference across the gastric membranes and its clinical significance (lantern slides), Edmund N. Goodman (by invitation); b] The circulation of the spleen in relation to spherocytic jaundice (lantern slides), Allen O. Whipple; c] Cardio-pulmonary functional tests in surgery, Herbert C. Maier, André Cournand (by invitation). ¶ General discussion. ¶ Executive session.

FEBRUARY 10—*Neurology and Psychiatry*. Reading of the minutes. ¶ Presentation of cases—From the service of The Mt. Sinai Hospital, Israel S. Wechsler; Discussion, Sidney Gross. ¶ Papers of the evening— a] The aims and limitations of aptitude testing, Samuel P. Horton, Ph.D. (by invitation); Discussion by Gladys Tallman, Ph.D., Robert B. McGraw; b] Classification, diagnosis and treatment of spinal arachnoiditis, J. Lawrence Pool (by invitation); Discussion by Lewis D. Stevenson, Clement B. Masson, Charles Davison. ¶ Executive session.

FEBRUARY 10—*Joint Scientific Session Section of Pediatrics and the New York Heart Association* (Heart Committee of the New York Tuberculosis and Health Association. Papers of the evening— a] Prevention of rheumatic recurrences: a discussion of various measures now being used, Ann G. Kuttner (by invitation), Medical Director, Irvington House; b] Twenty-years observation of

children with rheumatic heart disease following convalescent care, Alexander T. Martin; c] Coagency in the approach to the problem of rheumatic heart disease, Edward S. Rogers (by invitation), Assistant Commissioner, Department of Health, State of New York. ¶ Discussion, Homer F. Swift, Katherine G. Dodge.

FEBRUARY 16—*Ophthalmology*. Instruction Hour: 7:00 to 8:00 o'clock—Conjunctivitis, Alson Braley (by invitation). ¶ Executive session—Reading of the minutes. ¶ Presentation of cases— a] Recession of the trochlea for cycloptopia (two cases), Donald W. Bogart; b] A case of a tumor of the iris root, E. M. Katzin; c] A case of lacerated lid with coloboma—plastic repair, Rudolf Aebli. ¶ Papers of the evening—a] The relation of field contraction to blood pressure in cases of chronic primary glaucoma, Algernon B. Reese, John S. McGavie (by invitation); b] Virus diseases in ophthalmology. Phillips Thygeson; Discussion, I. Givner.

FEBRUARY 17—*Joint Meeting Section of Medicine and the New York Society of Tropical Medicine*. Papers of the evening—a] Florence Nightingale and tropical and military medicine, Thomas T. Mackie, Visiting Physician, Roosevelt Hospital; b] Tropical medicine in United States military history, Henry E. Meleny, Hermann M. Biggs Professor of Preventive Medicine, New York University; c] Typhus fever, John S. Snyder, Rockefeller Institute. ¶ Executive session of the section.

FEBRUARY 18—*Genito-Urinary Surgery*. Reading of the minutes. ¶ Papers of the evening—a] Certain aspects of perinephritic infections (lantern slides), A. Raymond Stevens; b] Aneurysm of renal artery, C. G. Child (by invitation); c] Secondary hyperplasia of a parathyroid in renal insufficiency (report of a case), Allister McLellan, Irvin Balensweig; d] A possible relationship of lymphogranuloma and cystitis, Victor F. Marshall

(by invitation); e] Occurrence and treatment of neurogenic bladder following resection of the rectum, Harmon J. Truax (by invitation); f] The treatment of prostatic cancers with endocrine therapy, Archie Dean; g] Relief of bladder neck and prostatic obstruction by transurethral resection, Frederick McLellan (by invitation); h] Causes of unsatisfactory end-results following adequate prostatectomy, Gustavus A. Humphreys (by invitation); i] Movie films demonstrating the physiology of spermatozoa, Robert Hotchkiss (by invitation). ¶ Discussion.

FEBRUARY 18—*Otolaryngology*. Reading of the minutes. ¶ Paper of the evening—Recent developments in chemotherapy, William D. Province (by invitation); Discussion by James G. Dwyer, J. Winston Fowler, Mervin C. Myerson, Arthur Palmer. ¶ General discussion. ¶ Executive session.

FEBRUARY 20—*Orthopedic Surgery*. Reading of the minutes. ¶ Presentation of case report—A case of static progressive spondylolisthesis, Nicholas S. Ransohoff. ¶ Papers of the evening—a] Double clothes-pin graft of the spine in spondylolisthesis and where laminar defects exist, David M. Bosworth; b] Traumatic spondylolisthesis, a report of three unusual cases in adults, Samuel Kleinberg, Michael S. Burman (by invitation). ¶ Discussion, Mather Cleveland. ¶ General discussion. ¶ Executive session. ¶ Honor guest and speaker, Dr. Luther Vargas, Brazilian orthopedist and son of the President of Brazil, addressed the Section on "Centro Medico Pedagogico, Oswaldo Cruz, of Rio de Janeiro."

FEBRUARY 21—*Obstetrics and Gynecology*—Program presented by Sloane Hospital for Women. Executive session—Reading of the minutes. ¶ Papers of the evening—a] Local application of estrogens in treatment of pruritus vulvae, Charles Lee Buxton (by invitation); b] Use of Miller-Abbot tube in obstetrics and gynecology, W. E. Pollard

(by invitation); c] Anatomical changes following radiation for carcinoma of the corpus uteri, James A. Corscaden; d] Mechanisms for face and brow presentations, D. Anthony D'Esopo (by invitation). ¶ General discussion.

MARCH 3—*Dermatology and Syphilology*. Presentation of cases—a] City Hospital; b] New York Polyclinic Medical School and Hospital; c] Metropolitan Hospital. ¶ Discussion. ¶ Executive session, appointment of Nominating Committee.

MARCH 6—*Combined Meeting: Medicine and Surgery*. Reading of the minutes. ¶ Papers of the evening—a] The treatment of chronic arthritis with special reference to the use of gold salts in rheumatoid arthritis, Martin Henry Dawson; b] Surgical procedures found useful in treatment of rheumatoid arthritis (motion pictures), M. N. Smith-Petersen (by invitation); c] The treatment of Marie-Strumpell arthritis of the spine, William Sheppard (by invitation). ¶ General discussion. ¶ Executive session, appointment of Nominating Committee for each Section.

MARCH 10—*Combined Meeting: Neurology and Psychiatry and the New York Neurological Society*. ¶ Presentation of case—Paraphenylendiamine poisoning and the central nervous system, Charles Davison; Discussion by Moses Keschner. ¶ Papers of the evening—a] The development of neurological surgery in New York City during the past twenty-five years—with remarks on the advances due to experiences in the first World War (illustrated by lantern slides), Charles A. Elsberg; b] Neuropsychiatric problems in burn encephalopathies of childhood, Lauretta Bender; Discussion by Morris B. Bender. ¶ Executive session of the Section—a] Reading of the minutes; b] Appointment of Nominating Committee.

MARCH 11—*Historical and Cultural Medicine*. ¶ Executive session—Nomination

of Section Officers and one member of Advisory Committee. ¶ Papers of the evening—a] The early history of auscultation and the stethoscope, Walter B. Mount; b] Selections from the Wolfe Collection of illustrations of noted men, Wardner D. Ayer (by invitation). ¶ Discussion.

MARCH 12—*Pediatrics*. ¶ Executive session—a] Reading of the minutes; b] Appointment of Nominating Committee. ¶ Papers of the evening—a] The management of acute obstructive laryngotracheobronchitis from the pediatric standpoint, A. Harry Neffson (by invitation); b] The treatment of pertussis, Lewis Jacobs (by invitation); c] The early management of poliomyelitis with an evaluation of the Sister Kenny Treatment, Mary M. I. Daly (by invitation), Jerome Greenbaum (by invitation), Edward Reilly (by invitation), Alvah Weiss (by invitation).

MARCH 16—*Ophthalmology*. ¶ Instruction Hour: 7:00 to 8:00 o'clock; The use of the Cross Cylinder, Willis Knighton. ¶ Exhibit—Types of strabismus, James W. White, Harold W. Brown. ¶ Executive session—a] Reading of the minutes; b] Appointment of Nominating Committee. ¶ In memoriam—Julius Wolff, Charles H. May. ¶ Presentation of cases—a] A case of hypertelorism, Henry O. Little (by invitation); b] A case of Coates' disease, A. L. Kornzweig (by invitation); c] A case of nevus verrucosus of the scalp with involvement of the conjunctiva, A. Russell Sherman; Discussion by Milton L. Berliner. ¶ Papers of the evening—a] Multiple sclerosis as an etiological factor in retrobulbar neuritis, William L. Benedict, Rochester, Minnesota (by invitation); Discussion by Tracy Putnam; b] Eye dominance, its nature and treatment, Ira Wile.

MARCH 18—*Genito-Urinary Surgery*. ¶ Executive session—a] Reading of the minutes; b] Appointment of Nominating Committee. ¶ Papers of the evening—

a] An unusual case of renal carbuncle in a child, Joseph Tenenbaum; b] Primary carcinoma of the male urethra, Stanley Woodruff; c] Anuria and stone formation following sulfadiazine therapy, Howard Jeck, L. A. Orkin (by invitation); d] Evaluation of renal function tests in surgery, Mark Fishberg (by invitation); Discussion by Henry Bugbee and Abraham Hyman.

MARCH 18—*Otolaryngology* (in joint session with the Section on Otolaryngology of the College of Physicians of Philadelphia) Reading of the minutes. ¶ Papers of the evening—a] The specialist in the Army, Lieutenant Alfred W. Doust, M.C., U.S.A. (by invitation); b] Otolaryngological aspects of aviation, Lieutenant Commander Leon D. Carson, M.C., U.S.N. (by invitation); c] War casualties in the Navy, Captain Reynolds Hayden, M.C., U.S.N., former commanding Officer, Naval Hospital, Pearl Harbor (by invitation). ¶ General discussion. ¶ Executive session of the Academy Section, Appointment of Nominating Committee.

MARCH 20—*Orthopedic Surgery*. Reading of the minutes. ¶ Presentation of Apparatus—Demonstration of "hand holder," Edgar D. Oppenheimer. ¶ Papers of the evening—a] Open reduction and implantation of bone chips for ununited fracture of the femoral neck (5 cases), Halford Hallock; b] Ununited fractures, Fred H. Albee; Discussion by Lewis Clark Wagner. ¶ General discussion. ¶ Executive session, appointment of Nominating Committee.

MARCH 24—*Obstetrics and Gynecology*. ¶ Executive session—a] Reading of the minutes; b] Appointment of Nominating Committee. ¶ Presentation of Cases*—a] Chronic inversion of the uterus; b] Ovarian pregnancy, William E. Alsop (by invitation). ¶ Papers of the evening—a] End-results in cancer of the ovary*, H. C. Taylor, Jr., A. V. Greeley; b] A follow-up evaluation of the Richardson Composite Operation for uterine

prolapse, Richard W. TeLinde, Chief Gynecologist, Johns Hopkins Hospital (by invitation); Discussion by Albert H. Aldridge. ¶ General discussion.

*Case reports and paper (a) presented by members of Gynecological Staff of Roosevelt Hospital.

AFFILIATED SOCIETIES

FEBRUARY 16—*New York Roentgen Society* (in affiliation with The New York Academy of Medicine). Papers of the evening—a] The role of the roentgenologist in orthopedic surgery, Samuel Kleinberg; b] X-ray diagnosis in early epiphyseolysis, Leo Mayer; c] Roentgenographic aids in the treatment of scoliosis, Samuel A. Jahss (by invitation); d] Skeletal changes in chronic renal insufficiency, Maurice M. Pomeranz. ¶ General discussion. ¶ Executive session.

FEBRUARY 26—*New York Pathological Society* (in affiliation with The New York Academy of Medicine). Presentation of cases—a] Syphilis of the aorta and coronaries, George Strassman, Philip Goldstein (by invitation); b] Squamous cell carcinoma of the bronchus and spindle cell sarcoma of the lung, Daniel A. Rock (by invitation), John W. Hall (by invitation). ¶ Papers of the evening—a] Liver lesions caused by excess ingestion of sulphur-containing amino acids, Joseph Victor (by invitation), David P. Earle, Jr. (by invitation); b] Agnogenic myeloid metaplasia of the spleen, Carl Reich, James Lisa. ¶ Executive session.

AFFILIATED SOCIETIES

MARCH 16—*New York Roentgen Society* (in affiliation with The New York Academy of Medicine). Paper of the evening—Certain diagnostic problems in the roentgenological examination of the esophagus, Richard Schatzki (by invitation). ¶ General discussion opened by Ross Golden. ¶ Executive session.

MARCH 26—*New York Pathological Society* (in affiliation with *The New York Academy of Medicine*). ¶ Papers of the evening—a] Benign chondroblastoma of bone: remarks on the so-called calcifying or chondromatous giant cell tumor, Louis Lichtenstein, Henry L. Jaffe; b]

Benign and malignant mammary alterations produced in the rat by methylcholanthrene and crystalline estrogen, Milton J. Eisen; c] Spontaneous solitary and multiple mast cell tumors (mastocytomas) in dogs, Frank Bloom. ¶ Executive session.

DEATHS OF FELLOWS

FINKLE, PHILIP: 1000 Park Avenue, New York City; born in Hartford, Connecticut, November 2, 1894; died in Miami Beach, Florida, March 13, 1942; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1918; elected a Fellow of the Academy May 7, 1931.

Dr. Finkle was adjunct physician and physician-in-charge of the arthritic clinic at The Mount Sinai Hospital and was engaged in medical research. He was a Fellow of the American College of Physicians and a member of the State and County Medical Societies.

FISCHER, CARL FERDINAND HERMANN: 35 East 84 Street, New York City; born in Clausthal, Province of Hannover, Germany, April 24, 1871; died in New York City, March 5, 1942; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1896; elected a Fellow of the Academy February 6, 1908.

Dr. Fischer joined the Lenox Hill Hospital staff in 1896 and for the past six years served in the capacity of consulting surgeon and head of the department of medical education. He was professor of clinical surgery at New York University College of Medicine, 1931-36; lecturer on clinical surgery at the College of Physicians and Surgeons, Columbia University, 1911-15; lecturer on clinical pathology at Polyclinic Medical School and Hospital, 1900-03; and

for a number of years was consulting surgeon to the Rockaway Beach Hospital. He was a Fellow of the American College of Surgeons, a member of the American Association for Thoracic Surgery, the New York Surgical Society, and the State and County Medical Societies.

GARVIN, WILLIAM CREIGHTON: Binghamton, New York; born in Philadelphia, Pennsylvania, November 30, 1873; died in Binghamton, April 3, 1942; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1903; elected a Fellow of the Academy November 2, 1922.

Dr. Garvin was superintendent of the Binghamton State Hospital, a Fellow of the American Medical Association, a member of the American Psychiatric Association, a member of the American Psychopathological Association, and a member of the State and County Medical Societies.

GREENWALD, HARRY MORDECAI: 499 Ocean Avenue, Brooklyn, New York; born in Unguar, Hungary, March 18, 1890; died in Brooklyn, March 15, 1942; graduated in medicine from Bellevue Medical School, New York University (now New York University College of Medicine) in 1910; elected a Fellow of the Academy April 6, 1933.

Dr. Greenwald was attending pediatrician to the Israel Zion Hospital and chief pediatrician to the Trinity Hospital. He was a diplomate of the American Board of Pediatrics, a Fellow of the American Medical Association, a member of the American Academy of Pediatrics, and a member of the State and County Medical Societies.

HIRSCH, ISAAC SETH: 133 East 58 Street, New York City; born in New York City,

December 3, 1880; died in New York City, March 24, 1942; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1902; elected a Fellow of the Academy February 6, 1913.

Dr. Hirsch was professor of radiology at New York University College of Medicine; x-ray consultant to the New York State Compensation Commission; and director of radiology at New York University Clinic and Beth Israel Hospital. From 1914 to 1917, he was professor of roentgenology at New York Post-Graduate Medical School and Hospital; and from 1910 to 1926, he was director of the department of radiology at Bellevue Hospital. In 1920, Cambridge University (England) awarded him a diploma in radiology. He was a diplomate of the American Board of Radiology, a Fellow of the American College of Physicians, a Fellow of the American Medical Association, a member of the Radiological Society of North America, Inc., and its vice-president in 1927-28, and a member of the State and County Medical Societies.

Dr. Hirsch was the author of "Principles and Practice of Roentgenological Technique," 1920; and "Principles and Practice of Roentgen Therapy," 1923. Besides his numerous writings, he served as associate editor and director of the department of technique and new devices of the American Journal of Electrology and Radiology.

In 1917 he entered the Medical Corps of the United States Army as Captain and later was promoted to the rank of Major.

JOHNSON, FREDERIC MORTIMER, JR.: 25 Morris Street, Yonkers, New York; born in New York City, August 5, 1874; died in Yonkers, New York, April 13, 1942; graduated in medicine from Syracuse University College of Medicine in 1904; elected a Fellow of the Academy February 3, 1910.

Dr. Johnson was attending gastroenterologist to the St. John's Hospital at Riverside, a diplomate of the American Board of Internal Medicine, a Fellow of the American Medical Association, a member of the National Gastroenterological Association, and a member of the State and County Medical Societies.

JUDD, ASPINWALL: 50 East 75 Street, New York City; born in St. Louis, Missouri, in 1868; died in New York City, March 17, 1942; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1896; elected a Fellow of the Academy May 19, 1904. He was a Fellow of the American Medical Association and a member of the State and County Medical Societies.

MCNEILL, WALTER HAROLD, JR.: 115 East 61 Street, New York City; born in Brooklyn, New York, November 13, 1886; died in New Rochelle, New York, March 22, 1942; graduated in medicine from Cornell University Medical College in 1910; elected a Fellow of the Academy February 1, 1917.

Dr. McNeill was clinical professor of the department of urology at New York University College of Medicine; attending urologist to Bellevue Hospital, the Welfare Hospital for Chronic Diseases, the Mount Vernon Hospital and the New Rochelle Hospital; and consulting urologist to the French Hospital and New York Central Railroad. He was a diplomate of the American Board of Urology, a Fellow of the American College of Surgeons, a Fellow of the American Medical Association, and a member of the American Urological Association, and the State and County Medical Societies.

MOORE, ALBERTUS ADAIR: 140 East 54 Street, New York City; born in Camden, South Carolina, June 26, 1876; died in New York City, March 23, 1942; graduate in medicine from the Medical College of the State of South Carolina in 1896; elected a Fellow of the Academy April 1, 1909. He was a Fellow of the American Medical Association and a member of the State and County Medical Societies.

ROBINSON, DAISY MAUD ORLEMAN: Meridale, New York; born in Fort Riley, Kansas, November 6, 1869; died in Jacksonville, Florida, March 12, 1942; graduated in medicine from the Medical Department, Columbian Medical College (now George Washington University School of Medicine), Washington, D. C., in 1890; elected a Fel-

low of the Academy, May 6, 1897.

Dr. Robinson was associated with the New York State Department of Health and with the U. S. Public Health Service in Washington. She was a member of the Société française de dermatologie et de syphiligraphie, being the first woman elected to membership in this Society, and a member of the State and County Medical Societies.

SKEEL, HARRY ROBERTSON: 115 East 61 Street, New York City; born in New York City, October 4, 1885; died in Riverdale, New York, March 22, 1942; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1913; elected a Fellow of the Academy April 6, 1933.

Dr. Skeel was surgical director of ophthalmology at the Manhattan Eye, Ear and Throat Hospital, and consulting ophthalmologist to the Bronx Eye and Ear Hospital. He was a Fellow of the American Medical Association, a member of the Association for Research in Ophthalmology, Inc., and a member of the State and County Medical Societies.

STEARNS, HENRY SCHERMERHORN: 655 Park Avenue, New York City; born in Yonkers, New York, December 4, 1861; died in New York City, April 2, 1942; graduated in medicine from the Medical Department of the University of the City of New York in 1884; elected a Fellow of the Academy June 6, 1889. He was a member of the New York County Medical Society, and its president, 1904-1905, a member of the State Medical Society, and a Fellow of the American Medical Association.

WALKER, JOHN BALDWIN: 117 East 72 Street, New York City; born in Lodi, New Jersey, January 16, 1860; died in New York City, April 13, 1942; received the degree of B.A. from Harvard University in 1884; graduated in medicine from Harvard Medical School in 1888; elected a Fellow of the Academy March 2, 1893; and served the Section of Surgery as its Secretary from 1896 to 1901 and as its Chairman from 1901 to 1903.

After three years of postgraduate work in Europe, Dr. Walker joined the staff of the New York Polyclinic Medical School and Hospital in 1894, and from 1897 to 1910 he served this institution as instructor in operative surgery. He was professor of clinical surgery at the College of Physicians and Surgeons, 1910-1938; and for many years consulting surgeon to Bellevue and Manhattan State Hospitals and the Hospital for Special Surgery, formerly the Hospital for the Ruptured and Crippled. He was a Fellow of the American College of Surgeons, and a member of the American Medical Association, the American Surgical Association, the State and County Medical Societies and a member of the Société internationale de chirurgie.

Dr. Walker was the author of "Volume IX—Hernia" in "Twentieth Century Practice of Medicine," and contributed many papers on the operative treatment of fractures.

During the last war, Dr. Walker commanded Base Hospital 116 of the American Expeditionary Force in France and for his work was awarded the Distinguished Service Medal. He held the rank of Colonel in the Officers Reserve Corps.

BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE



JULY, 1942

THE ANTI-COAGULANTS
Heparin and the Dicoumarin-3, 3' Methylene-Bis-
(4-Hydroxycoumarin)*

ANDREW PRANDONI and IRVING WRIGHT

From the Department of Medicine of the New York Post-Graduate Medical School and Hospital,
Columbia University

THE problem of inhibition of coagulation has been the subject of numerous and frequently conflicting reports during the past two decades. From this material pertinent findings will be briefly reviewed in order to present a background for the consideration of Heparin and the Dicoumarin-3, 3' Methylene-Bis-(4-Hydroxycoumarin). The conclusions suggested should probably be considered as representing current opinion rather than final truth.

Prothrombin, a protein normally present in the blood plasma in a concentration of approximately 40 mg. per cent,¹ is quantitatively converted into thrombin by the action of thrombokinase and ionic calcium.

Prothrombin is the component chiefly affected by 3, 3' methylene-bis-(4-hydroxycoumarin),² a clotting inhibitor which will be discussed at length later. We shall, therefore, dwell upon it briefly. The liver is

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the chief source of prothrombin.^{3, 4, 5, 6} Vitamin K appears to be important in its formation.

Hypoprothrombinemia may occur in conditions associated with insufficient vitamin K intake, absorption and utilization. Reduction in prothrombin concentration to below 35 per cent of normal, will, in many instances, produce a hemorrhagic state. Avitaminosis K on the basis of dietary insufficiency rarely occurs, possibly due to the capacity of the intestinal flora to synthesize the vitamin when such a deficiency exists.⁷ Absorption of vitamin K is contingent upon an adequate concentration of bile salts in the gastrointestinal tract,^{8, 9} hence obstructive jaundice and biliary fistulae are frequent causes of hypoprothrombinemia. Diminished prothrombin concentration occurs in ulcerative colitis, sprue, intestinal obstruction and polyposis,^{10, 11, 12, 13} due to interference with absorption of vitamin K through the intestinal wall.

Prothrombin deficit despite adequate vitamin K intake and absorption may occur in hepatic derangements.^{13, 14, 15, 16, 17, 18} Hepatic intoxications (due to carbon tetrachloride,¹⁹ chloroform,³ and phosphorus), hepatectomy⁵ and extensive liver damage on other bases^{13, 17, 18} result in a hypoprothrombinemia in no way influenced by the administration of large doses of vitamin K. DeLor and Reinhart²⁰ observed prothrombin to be universally diminished when liver function fell below 50 per cent, as determined by the hippuric acid method.

Calcium, as ionic calcium, hastens the conversion of prothrombin to thrombin.²¹ For calcium deficiency to significantly inhibit coagulation, however, serum calcium would have to fall below the lowest recorded level compatible with life.²²

Thrombokinase is a lipoprotein closely allied to cephalin. In combination with calcium it is considered by Eagle²³ to constitute a proteolytic enzyme analogous to trypsin, which reacts with prothrombin to form thrombin. Crude or crystalline trypsin²⁴ and proteolytic snake venoms²⁵ can be substituted for calcium-platelet or calcium-tissue-extract mixture in the activation of prothrombin in vitro. The view that activation of prothrombin involves proteolysis would seem to be supported by these reactions. Thrombokinase is present in all tissues; the lung, platelets, and brain being its richest sources. Thrombokinase affects only the velocity of the prothrombin to thrombin conversion not the quantity of the thrombin derived from prothrombin.^{26, 42} Heparin antagonizes thrombokinase,²⁷ blood remaining fluid despite the presence

of large quantities of circulating prothrombin and fibrinogen, only as long as the thrombokinase-heparin balance is maintained in favor of heparin, and in all probability certain other anti-coagulants about which little is known.

Thrombin, a protein, is probably a hydrolytic product of prothrombin. Schmidt^{28,29} and Eagle³⁰ believe it to be a proteolytic enzyme which converts fibrinogen into fibrin. Thrombin is capable of converting 2000 times its weight of fibrinogen into fibrin.³⁰ It may be replaced in the conversion of fibrinogen to fibrin by proteolytic enzymes such as papain²⁴ and numerous snake venoms (*Crotalus adamantus*, *Crotalus terrificus*, *Crotalus horridus*, *Bothrops nummifera*, etc.).²⁵ No apparent stoichiometric relationship exists between thrombin and fibrinogen.

Fibrinogen is a globulin-type protein of special solubilities. It is produced exclusively in the liver. Except in very severe forms of liver disease, the fibrinogen concentration in the blood is maintained at a normal level of 0.2 to 0.3 mg. per cent. Its conversion from the physical state of a disperse hydrosol to a quasi-crystalline fibrin gel is the *sine qua non* of natural blood clotting.

In vivo, anti-coagulants may be arbitrarily grouped in five classes:

1. Substances in nature which have anti-coagulant activity when added to blood; for example, hirudin, an anti-thrombin^{31,32} and anti-kinase,³³ derived from the buccal gland of the leech, and snake venoms of the cobra venom type.

2. Anti-coagulant substances isolated from blood or tissue, e.g., heparin.

3. The physiological anti-coagulant presumed to be present because of delayed coagulation of the blood. This is believed by some to be heparin.³⁴ Others contend that it is an anti-thrombin distinct from heparin.

4. Substances which, when ingested, either depress formation of one of the components of the coagulation mechanism or render it inactive, e.g., dicoumarin.

5. Synthetic substances, which, when added to blood, inhibit coagulation; e.g., the diazo dyes (Chicago blue, chlorazol fast pink, sodium thiosulfate, trypan blue), germanin and liquoid.^{35,36,37,41,50}

Since it is beyond the scope of this paper to discuss in detail the mechanism of, and the clinical results obtained with each of these substances, the major portion of the discussion will be devoted to heparin,

and dicoumarin, a recently isolated clot inhibitor which has been the subject of investigation in the Department of Medicine of the New York Post-Graduate Medical School and Hospital during the past year.

The limitations of hirudin which render its clinical use impracticable are its low potency, as compared to heparin, and its limited supply.

The synthetic *in vivo* anti-coagulants are similar to heparin in their mode of action.³⁸ With the exception of chlorazol fast pink, a very narrow margin exists between the therapeutically effective and the toxic dose. The anti-coagulant activity of chlorazol fast pink has been found to be 10 to 15 times less than that of heparin.

HEPARIN

Heparin is a strongly acidic compound containing mucoitin polysulfuric acid, acetic and glycuronic acid plus a base glucosamine.³⁹ It inhibits the coagulation of blood *in vitro* or *in vivo* by retarding the conversion of prothrombin to thrombin, and by direct antithrombic activity.⁴² Heparin arises in the mast cells of Ehrlich⁴⁰ which are found chiefly in the vicinity of the finer blood vessels.⁴⁰ Jorpes³⁴ concluded from the location of the mast cells that they constitute a hormonal system feeding heparin to the blood. The liver capsule and the lung are the richest reservoirs of heparin in the body. Appreciable amounts have also been extracted from the subcutaneous tissue and the blood vessels. Histologically, heparin inclusions in the mast cells may be detected by the characteristic metachromatic stain which they yield with toluidine blue.

Ferguson⁴² has demonstrated that heparin possesses two distinct actions in the first phase of the clotting mechanism. First, it retards the rate of prothrombin conversion to an extent which is inversely proportional to the amount of the thrombokinase present. Second, there is an effect on the amount (effectiveness) of the thrombin formed.⁴³ Heparin apparently not only inhibits coagulation by retarding the formation of thrombin, but also by acting as an anti-thrombin.^{22, 44, 45} Quick,⁴⁶ Brinkhous,⁴⁷ Jaques and Mustard⁴⁸ have demonstrated that heparin is only active in the presence of a co-factor which is part of the albumin fraction. In their opinion, heparin combines with and enhances the action of normal plasma anti-thrombin. Trypsin⁴⁹ and thrombokinase²⁷ directly antagonize heparin, coagulation being prevented unless an excess of these substances is present. Many clot inhibitors resemble heparin

in their mode of action and in the presence of sulfur in the molecules. For example, sulfo-cellulose, hermophenyl, liquoid, germanin, diazo dyes, cystine, and sodium thiosulfate, like heparin, exhibit an anti-coagulative activity proportional to their sulfur content.^{38,39,40,50} Lindgren and Wilander⁵¹ and Hedenius⁵² observed that with heparin the coagulation time may be maintained at optimal levels of twenty to thirty minutes without influencing the bleeding time as determined by the Ivy method. Best⁵³ demonstrated, by means of a glass cell technique, that platelet agglutination, as well as fibrin deposition, was inhibited by heparinization. Subsequently, Solandt and Best⁵⁴ presented evidence that very extensive injury to the arteries and veins never resulted in a maximal stimulus to platelet agglutination. The amount of heparin required to prevent platelet thrombi in vivo was found to be much smaller than that required to prevent the process in a glass cell. Salmine-sulfuric acid, a protamine, neutralizes the effect of twice the amount of heparin in vitro and in vivo. An intravenous injection of this protamine will immediately check any undesirable bleeding produced by heparin.^{55,56}

Preparations: The products available for clinical use are:

1. Heparin—Lederle 10 cc. vial—10 mg./cc.—1100 Toronto u/cc.
2. Liquemin—Roche Organon 10 cc. vial—10 mg./cc.—1100 Toronto u/cc.
3. Solution of heparin—Connaught Laboratories 10 cc. vial—10 mg./cc.—1100 Toronto u/cc.

These products are at present so standardized that each cc. keeps 5000 cc. of plasma in vitro in a liquid state for four hours at 37° C.

Methods: The methods of heparinization in use today are local, regional and general. Local and regional heparinization are used chiefly in vascular surgery in order to confine the anti-coagulant effect to the operative area. In the treatment of thrombosis and thrombo-embolic conditions, general heparinization is the method of choice. This may be achieved by either of two techniques: (1) By the continuous intravenous drip; and (2) by multiple intravenous injection. In the first, advocated by Best and Murray and utilized widely in this country, the appropriate amount of heparin is added to an infusion which is permitted to flow continuously throughout the course of therapy into the selected vein. The choice of diluent may be modified by the individual case, heparin being equally active in five per cent glucose solution,

normal saline, or Ringer's solution. Should fluid restriction be imperative, the entire daily dose may be given in as little as 800 to 1000 cc. The amount of heparin required to secure an arbitrary optimal prolongation of coagulation time, namely, twenty to thirty minutes, varies according to the response of the individual patient. Twenty to thirty mg. per hour usually suffice to maintain this level. Variation in response in different patients and in the same patients from day to day will of necessity modify the dose. In our opinion coagulation times in excess of forty minutes are hazardous. Maintenance of a coagulation time of twenty to thirty minutes is insured by repeated estimations of the venous blood clotting time at four hour intervals by means of the Lee-White two tube method. The intermittent intravenous injection method has been used almost exclusively by Crafoord,⁵⁷ Jorpes,³⁴ and Lindgren and Wilander⁵¹ since 1936. These observers have been using doses of from 50 to 75 mg. three times daily at 8 A.M., noon and 4 P.M. with an evening dose of 100 to 125 mg. at 8 P.M. Appropriate adjustments in the dosage are made as indicated by the coagulation time obtained. The marked fluctuations in coagulation time encountered with this method render dosage estimation problematical. Dosage should theoretically be so regulated that the coagulation time never falls below 15 minutes, but this is very difficult to achieve with this technique. The disadvantage of multiple venipuncture may be obviated by employing a specially constructed needle designed by Olovson.⁵⁸ This needle is allowed to remain in situ throughout the course of therapy. It is supported by an aliform plate which is fixed to the arm by adhesive tape and is provided with a detachable cap with a rubber membrane through which the injections may be made even while the patient is sleeping. Coagulation has never been observed in the needle during the course of treatment.⁵⁹

Certain theoretical disadvantages are inherent in this method of heparin administration. Chief among these is the impossibility of maintaining the more or less constant elevation of coagulation time secured with the continuous intravenous drip. Secondly, the coagulation time immediately following injection of undiluted heparin attains levels, which may be hazardous, of one hour or more. Subsequent to the initial abrupt rise, there is a steady fall over a four hour interval to as low as eight to ten minutes in some cases. The foregoing drawbacks notwithstanding, these authors have reported satisfactory results with the intermittent intravenous injection technique.

Heparin has also been administered by the subcutaneous route. The magnitude of the doses required to obtain the desired levels with this method renders it impracticable.

Because of the voluminous available literature concerning the indications for the therapeutic and prophylactic use of heparin, we shall confine ourselves to a brief summary of recent clinical and experimental developments. Regional and general heparinization have proved invaluable in maintaining vessel patency following arteriotomy for the removal of thrombi and emboli. Murray,⁶⁰ Lam,⁶¹ Lindgren and Wilander⁵¹ have reported successful embolectomies with this technique. Pratt, of our service, has obtained similar results with heparin in six embolectomies and in twelve other instances of vascular surgery, hitherto usually unsuccessful because of the rapidity with which the repaired vessel became obstructed by thrombi, during the postoperative period. In mesenteric thrombosis, with a mortality rate of from 85 to 95 per cent, heparin was employed successfully by Murray^{60,62} in six cases. Ravdin⁶³ reported comparable results in two instances. Holmin and Ploman⁶⁴ demonstrated that heparinization of patients with thrombosis of the central retinal vein appreciably reduced the incidence of blindness following this disease. This observation has been confirmed by Boström and Olsson,⁶⁵ Rea⁶⁶ and other ophthalmologists. Whipple⁶⁷ and Murray⁶⁸ observed that postoperative heparinization will prevent the portal thrombosis which frequently follows splenectomy for Banti's syndrome and familial jaundice. Recovery in patients with massive pulmonary embolization appears to be influenced by heparin therapy. The authors have successfully treated five such patients in whom the initial prognosis was extremely grave. Murray,⁶⁸ Ravdin,⁶³ Clason,⁶⁹ Rosenqvist⁵⁹ and Priestley⁷⁰ have reported similar experiences, observing likewise a marked diminution in morbidity as well as mortality. The fact that spontaneous recovery does occur in approximately 12.2 per cent of cases of pulmonary embolization, according to Barker's⁷¹ statistics, renders observation of a large series desirable before any conclusion can be drawn as to the efficacy of this form of therapy. The treatment of subacute bacterial endocarditis with heparin and sulfonamide derivatives has yielded encouraging results in a few of the cases reported by Kelson and White.⁷² In the case reported by Dock-eray and Kawerau,⁷³ which terminated in a fatal cerebral hemorrhage, heparin was only of transient value. Other reports^{74,75,76,77} which ap-

pear in the literature reveal that fatal cerebral hemorrhage following embolization not infrequently occurs in patients receiving combined heparin and sulfanilamide therapy for subacute bacterial endocarditis. The value of this combined therapy is yet to be determined. It has failed in nine cases on our service.

The value of heparin therapy in coronary thrombosis is still speculative. Solandt and Best⁷⁸ showed that preliminary heparinization will prevent thrombosis of coronary arteries injected with sodium ricinoleate. This work seems to indicate that if administered early, and in adequate dosage, heparin may minimize or inhibit propagation of the thrombus. At present, however, the prevention of mural thrombi seems to be its sole virtue in this disease.

Lyons,⁷⁹ Schall,⁸⁰ Ershler and Blaisdell⁸¹ have reported the successful treatment of cavernous sinus thrombosis by combining heparin with chemotherapy.

Marked improvement in a single case of thrombosis of the posterior inferior cerebellar artery (Wallenberg syndrome) following heparinization has been reported by Magnusson.⁸²

In a series of 627 patients reported by Crafoord,^{57,83} 325 who had received heparin prophylactically during the postoperative period showed a complete absence of thrombo-embolic phenomena. The remaining 302 patients subjected to comparable operative procedures, who had not received the anti-coagulant, showed an incidence of thrombo-embolic complications of approximately 9 per cent. (This figure is considerably greater than that encountered in this country.) Nine of this latter group died. Diagnosis was confirmed by autopsy. Similar observations supporting the efficacy of heparin as a prophylactic against thrombosis following obstetric and gynecologic procedures have been reported by Wetterdal,⁸⁴ Leissner⁸⁵ and others.

The numerous variations in the clinical picture accompanying thrombophlebitis, and the frequently insidious onset of this condition account in some measure for failure of its early detection. Most cases, if diagnosed in their incipiency, respond favorably to heparinization. Localization of the thrombus to its original site, accompanied by marked diminution in embolic complications, morbidity and mortality, are the advantages reported by numerous observers. On the other hand, the difficulty inherent in its use, together with other objections to be discussed later, have led many groups to confine its use

in thrombophlebitis to those patients who have suffered one pulmonary embolus. Venography in suspected cases, according to Bauer's⁸⁶ recent report, gives promise of affording a means of earlier and more certain recognition of incipient thrombophlebitis.

An interesting recent development in heparin therapy, while not related to the cardiovascular system, is worthy of mention. This is the prevention of adhesions by instillation of heparin into the peritoneal cavity of rabbits subjected to contamination and trauma.⁸⁷ In dogs, the recurrence of divided adhesions was 6 times greater in the non-heparinized group as compared to that in heparinized animals. Wright and Hinton⁸⁸ have tried this in man with apparently good results. Definite conclusions as to the efficacy of intraperitoneal heparinization in man cannot yet be drawn inasmuch as no opportunity to reexamine the abdominal cavity has presented itself. Some danger of hemorrhage following closure does exist, when the initial contraction of the small vessels wears off three to four hours postoperatively; hence routine use of heparin intraperitoneally is not to be recommended at this time.

There exists some difference of opinion as to how long heparin therapy should be continued. Following vascular surgical procedures in which the lumen is kept patent by heparinization, the site of arterial suture has been found experimentally⁶³ to be healed after 72 hours. Murray⁶⁸ and Lindgren⁵¹ prefer to continue heparinization postoperatively until the patient is out of bed. In thrombophlebitis Bauer⁸⁶ discontinues therapy after five days in abortive cases; in certain instances he has withheld heparin as soon as the temperature and pulse returned to normal. Hedenius⁵² proposed four days as the minimum effective period of therapy. In our experience such periods have frequently proven too short. In the majority of cases of thrombophlebitis the intravascular inflammatory process persists despite inhibition of thrombus propagation. We feel, therefore, that in order to minimize the tendency to relapse the administration of heparin in quantities adequate to maintain coagulation time at optimum levels should be continued over a period of from twelve to fourteen days. Withdrawal of heparin is followed by a so-called negative phase during which the blood exhibits increased coaguability. For this reason heparin should never be discontinued abruptly but rather by a successive slow diminution in dosage. On our service the following criteria have been adopted as evidence of cessation of the intravascular process in thrombophlebitis: Return of

temperature and pulse to normal for one week; complete disappearance of local tenderness, pain, and erythema along the course of the involved vessel over a similar period of time; the sedimentation rate and leukocyte count, if elevated, should likewise return to and maintain a normal level for one week; reduction of edema to a minimum is desirable. Strict adherence to the above routine has reduced, but not eliminated, the incidence of reactivation of the acute process after discontinuing heparin. As a rule, the briefer the period of heparinization the greater the possibility of recurrence. Reactivation of acute thrombophlebitis may definitely occur following heparinization. In an experience involving the heparinization of approximately 100 patients, the following examples have been encountered. Three patients in whom heparin therapy was maintained for two to five days following satisfactory clinical evidence of subsidence, showed reactivation shortly after cessation. Two others had recurrences after heparinization for ten days; two more showed reactivation of the process following fourteen days of heparin therapy, one of whom suffered a second recurrence following an additional fourteen days of treatment. We have also seen two instances of non-fatal pulmonary embolization while heparin therapy was maintaining the clotting time at levels of twenty-six to thirty minutes.

Complications: In 315 cases reported by Murray and Best⁶⁸ four developed hematoma of the wound. Priestley, Essex and Barker⁷⁰ observed transient hematuria in several of their forty-five patients. Ershler and Blaisdell⁸¹ and Witts⁷⁶ reported the occurrence of massive hematuria following heparinization. Lam⁶¹ in his series of thirty cases noted evidence of a hemorrhagic diathesis in four patients. Kelson,⁷² Fletcher,⁷⁵ Friedman,⁷⁷ Witts⁷⁶ and Miller⁷⁴ have reported deaths as the result of cerebral hemorrhage following treatment of subacute bacterial endocarditis with heparin and sulfonamide drugs.

Although heparin is a valuable agent in anti-coagulant therapy, it does have certain disadvantages. Chief among these are:

1. Difficulty in administration with its attendant discomfort to the patient.
2. Costliness: Fifteen to twenty dollars worth of heparin is required daily in the average case.
3. Prolonged administration.
4. Occasional failures.

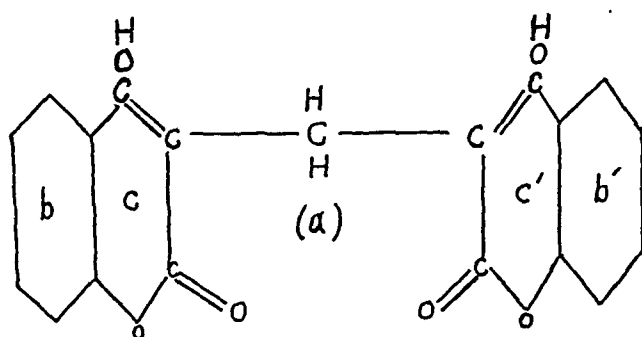


Fig. 1—Structural formula for dicoumarin 3, 3'-methylene-bis-(4-hydroxycoumarin).

Added to these are the dangers inherent in all types of anti-coagulant therapy, unless scrupulous control is observed.

DICOUMARIN*

The isolation and synthesis of the dicoumarin 3, 3' methylene-bis-(4-hydroxycoumarin) by Link⁸⁹ and his co-workers in 1940 provided a new and valuable substance for workers interested in the field of anti-coagulants. Rather exhaustive studies in which this substance has been administered to rabbits, dogs, and other animals have been reported by Link⁸⁹ and his co-workers, and by Bingham, Meyer and Pohle.¹⁰⁶ As may be anticipated from a consideration of the structural formula shown in Figure 1, 150 substitution and degradation products of 3, 3' methylene-bis-(4-hydroxycoumarin) have been isolated by Link's group,⁹⁰ more than 40 of which show anti-coagulant properties as measured by coagulation and prothrombin studies.

Dicoumarin 3, 3' methylene-bis-(4-hydroxycoumarin), when fed to susceptible animals, diminishes the clotting power of the blood and, in some cases, produces fatal hemorrhage. In nature, this compound occurs in spoiled sweet clover silage. It was for this reason that Roderick^{96,97,98} and Schofield^{94,95} used the name "sweet clover disease" to describe the hemorrhagic diathesis resulting in cattle from the ingestion of spoiled sweet clover hay. The coagulating power of the blood can be restored by discontinuing the administration of the hemorrhagic agent, or by injection of serum or whole blood freshly drawn from

* The Dicoumarin used in this study was supplied through the courtesy of Dr. Karl Paul Link, University of Wisconsin, and Dr. Y. Subbarow of the Lederle Laboratories.

cattle. Quick⁹⁹ confirmed Roderick's⁹⁷ observation that the coagulation defect in animals with sweet clover disease was due to a hypoprothrombinemia, the mechanism of which was, and still is, unknown.

Link^{89,90,91,92,93} and his co-workers completed the isolation and synthesis of this dicoumarin in April 1940. The pharmacological activity of 3, 3' methylene-bis-(4-hydroxycoumarin) has been established in animals by Link,¹⁰⁵ Bingham,¹⁰⁶ and Butt¹⁰⁷ with their associates. Link and his group have demonstrated that within certain limits, increasing the size of a single dose increases the degree and prolongs the time of reaction in standardized susceptible rabbits. These observers likewise demonstrated that dogs survived large single doses, whereas in some cases repeated divided doses aggregating less than the large single dose, produced toxicity and death. Link¹⁰⁹ suggests incomplete absorption from the gastrointestinal tract as an explanation of this variation in response.

Postmortem studies on animals that had succumbed to hemorrhage produced by the ingestion of spoiled sweet clover, were first made by Roderick⁹⁶ who noted that hemorrhage may occur in any part of the body, but most frequently at points of stress, in the subcutaneous and intermuscular fasciae. No changes in the blood vessels which could explain the hemorrhagic tendency were observed. Hemorrhage was, however, easily produced prior to death by surgical incision or by trauma. In October 1941, Bingham, Meyer and Pohle¹⁰⁶ reported the results of similar studies on twenty-five dogs which had received hemorrhagic doses of the synthetic dicoumarin. Their observations revealed that hemorrhage had occurred in the subcutaneous and intermuscular fasciae in all the animals and that gross gastrointestinal hemorrhage and bleeding into the pleural spaces and pulmonary parenchyma were frequently observed. Marked dilatation of capillaries, small arteries and veins was also noted. No lesions of the vessel walls were found which could explain the mechanism whereby the blood was extravasated. Another interesting observation made by these authors was the absence of significant gross or microscopic evidence of parenchymatous disease of the liver, kidney or other organs. Occasional moderate hydropic degeneration of the liver was observed, but nothing more. Hydropic degeneration is known to occur post mortem, depending upon the time which has elapsed between death and tissue fixation. Roderick had previously reported liver damage as an occasional pathologic finding

in cattle which died from this disease.

Studies on the response to 3, 3' methylene-bis-(4-hydroxycoumarin) administered orally to human subjects have been reported by Butt, Allen and Bollman,¹⁰⁷ Bingham, Meyer and Pohle¹⁰⁶ and the authors. Bingham¹⁰⁶ and his co-workers have also used the disodium salt of the dicoumarin intravenously. Characteristic prolongation of the prothrombin and coagulation times, similar to those observed in animals, have been noted, by all workers. The present report on the effects of the dicoumarin 3, 3' methylene-bis-(4-hydroxycoumarin) includes a description of the hemorrhagic complications which were encountered in our series in man, but which neither Bingham et al¹⁰⁶ nor Butt et al¹⁰⁷ have previously mentioned. An attempt has been made, therefore, to ascertain the nature of this variation in response.

Our objectives have been to study the reactions produced in man by this substance, the mechanism involved therein and to determine the minimum effective dose required in humans to produce an effect on the coagulation time comparable to that of heparin. In this the prothrombin reduction plays an important role. To date this dicoumarin has been administered to thirty-one patients. Detailed studies regarding twenty of these patients have been analyzed and embodied in this report. The age of the patients varied from 22 to 83 years. The distribution according to admission diagnosis is as follows:

| | |
|--|----|
| Thromboangiitis obliterans | 2 |
| Rheumatic cardiovascular disease | 2 |
| Thrombophlebitis | 4 |
| Arteriosclerosis obliterans | 12 |

Prior to administration of the medication, a thorough history was taken and a complete physical examination done in order to eliminate preëxisting hemorrhagic diathesis, and to avoid the possibility of causing uncontrollable bleeding from peptic ulcers, fibromyomata or other hitherto quiescent foci of potential hemorrhage.

Blood counts, including red and white cell counts with differential and hemoglobin determinations, were done on all cases before administration of the drug and at weekly intervals thereafter until prothrombin time returned to normal. Because of the wide variations obtained in platelet determinations during the control period and the feeling among hematologists that most platelet counts using available techniques are at best inaccurate, this procedure was discontinued after a trial.

Capillary fragility tests, using the method described by Wright and Lilienfeld,¹⁰⁸ were performed prior to administration of the dicoumarin, during the course of therapy, when prothrombin time exceeded 35 seconds, and when and if hemorrhagic manifestations appeared.

Sedimentation rates were determined by the Westergren¹¹⁰ method prior to administration of the drug and at weekly intervals thereafter.

Routine urinalysis was performed three times weekly during the control period and during administration of the dicoumarin.

An attempt to estimate renal status was made on the basis of urea clearance tests, blood urea and non-protein nitrogen ratio and renal concentration tests (2-hour method described by Mosenthal).¹¹⁷ These were done prior to administration of the medication with the object of reducing the possibility of retention toxicity, such as that encountered at times with other types of chemotherapy.

An evaluation of the *hepatic status* was made on the basis of the bromsulfalein test (Magath and Snell modification),¹¹⁶ plasma proteins, cholesterol ester ratio and cephalin flocculation test.

Gastric fractional analysis, using parenteral histamine, was done once during the period of observation, following the suggestion of Link¹⁰⁹ that gastric anacidity might hasten absorption of the dicoumarin.

Prothrombin time was determined daily, using the Fullerton¹¹¹ modification of the Quick technique. Normal plasma with this method gave values of 20 seconds plus or minus 2. Daily controls performed simultaneously served as a check on the activity of the thromboplastic substance used.

Coagulation time was estimated by the Lee-White¹¹⁵ two tube method with normals ranging between 5.5 and 7.5 minutes.

A three day control period preceded the administration of the drug in all cases. During this time base line coagulation and prothrombin times were ascertained.

Dosage: At the outset of our experiments no data on the dosage of this dicoumarin in humans were available. Anticipating the possibility of hemorrhagic complications, we began with doses which, on the body weight basis, were but a fraction of those which had produced prolongation of coagulation and prothrombin time in animals. Five patients received daily single, oral doses of 100 mg. for seven days followed by doses of 200 mg. at daily intervals for periods varying from four to eleven days. Of this group two patients received a total of 1500

mg. over an eleven day period; one patient a total of 1700 mg. over a twelve day period; and two a total of 2900 mg. over a period of eighteen days. Four patients received single oral doses of 200 mg. at twenty-four hour intervals for periods varying from four to eleven days. Total doses in this group were as follows: 800 mg., 1200 mg., 1800 mg., and 2200 mg.

Three patients received a series of four 300 mg. doses at twenty-four hour intervals and one patient a series of five 300 mg. doses, totaling 1200 and 1500 mg. respectively. The remaining patients received an initial dose of 600 mg. of the dicoumarin, followed in all but one case by daily doses of 200-300 mg. for periods varying from five to eight days. The amount of the dicoumarin administered to these patients total 600, 2200, 1800, 1800, 1500, 1500 and 2400 mg. The dose of the dicoumarin was administered in all instances at twenty-four hour intervals. Total dose of the body weight basis varied from 7.8 to 45.9 mg./kg.

Responses in the form of prolongation of the prothrombin and coagulation time varying widely in degree and duration were observed in patients receiving different doses and in different patients receiving the same total dose. We shall briefly outline the result of an analysis of the coagulation and prothrombin time curves obtained.

The initial effect manifested itself as a significant prolongation of prothrombin time which occurred in from one to five days, average 3.2 days. A change equivalent to three times the standard deviation for accuracy of the method was considered significant.

The maximal effect, namely, the greatest increase in prothrombin time following the first administration of dicoumarin, occurred in from one to twenty days, with an approximate average of thirteen days.

The coagulation time at the period of maximal prolongation varied from eight to thirty-three minutes, averaging thirteen minutes.

The maximal prolongation of prothrombin time ranged from twenty-six to seventy seconds, with an average of forty-seven seconds.

The total duration of effect, or time lapsing between the initial rise in the prothrombin time and its return to control level, was two to twenty-six days, averaging 11.2 days.

The duration of effect, after discontinuing the administration of dicoumarin, varied between one and twenty-three days, average 11.2 days. As a rule the degree and duration of prolongation of coagulation

TABLE I
SUMMARY OF FINDINGS ON PATIENTS IN WHOM A HEMORRHAGIC SYNDROME WAS PRODUCED BY DICUMARIN

| Case No. | Age | Total Dose | | Duration of Therapy | Day on Which Hemorrhage Appeared | Proth Time During Hemorrhage | Coag Time (Lee-White) During Hemorrhagic Episode | Duration of Hemorrhage Manifest. | Treatment | Signs and Symptoms |
|----------|-----|------------|-------|---------------------|----------------------------------|------------------------------|--|----------------------------------|--|---|
| | | gm. | mg/kg | | | | | | | |
| 1 | 25 | 1.5g | 27.2 | 11 days | 16 | 54-66 sec | 12-17 min | 4 days | Withdrawal of Dicoumarin | (1) Gingival bleeding (2) Weakness—Vertigo |
| 4 | 37 | 1.7g | 27.7 | 12 days | 14 | 34-53 sec | 15-16 min | 7 days | (1) Transfusion T. (2) Vitamin K.C.P. (3) Nicotinic Acid (4) Supportive | (1) Spontaneous hemorrhage from wound (2) Weakness (3) Gingival hemorrhage, sublingual ecchymosis (4) Hematuria (5) Subconjunctival hemorrhage (6) Hematemesis (7) Purpura |
| 5 | 45 | 2.9g | 36.4 | 18 days | 19 | 40-70 sec | 16-33 min | 5 days | (1) Transfusion T. (2) Vitamin K.C.P. (3) Nicotinic Acid (4) Supportive | (1) Spontaneous bleeding from wound (2) Weakness (3) Purpura over trunk and extremities (4) Hematuria (5) Pharyngeal & Sublingual ecchymoses (6) Subconjunctival & Gingival hemorrhage |
| 6 | 60 | 2.2g | 38.1 | 11 days | 12 | 34-48 sec | 14-18 min | 8 days | Withdrawal of Dicoumarin | (1) Spontaneous bleeding from wound (2) Purpura over trunk and extremities (3) Weakness and lassitude (4) Microscopic hematuria |
| 9 | 60 | 1.2g | 18.6 | 6 days | 12 | 48-56 sec | 12.5-23 min | 10 days | (1) Transfusion T. (2) Vitamin K.C.P. (3) Nicotinic Acid (4) Supportive | (1) Hematuria (2) Hematemesis (3) Sublingual ecchymosis (4) Epistaxis (5) Gingival hemorrhage (6) Weakness |
| 10 | 67 | 1.2g | 15.5 | 4 days | 12 | 40-42 sec | 11.5-13.5 min | 5 days | (1) Vitamin K.C.P. (2) Nicotinic Acid (3) Supportive | (1) Subconjunctival hemorrhage (2) Weakness—Vertigo (3) Epistaxis |
| 16 | 69 | 1.8g | 28.5 | 5 days | 16 | 38.5-53.5 sec | 22-26 min | 4 days | (1) Transfusion T. (2) Vitamin K.C.P. (3) Nicotinic Acid | (1) Syncope (2) Hematemesis (3) Purpura over trunk & extremities |
| 19 | 54 | 1.5g | 23.6 | 5 days | 5 | 38-40 sec | 10-17 min | 4 days | (1) Transfusion T. (2) Vitamin C.P. (3) Nicotinic Acid | (1) Hematemesis (2) Weakness |

and prothrombin time varied directly with the magnitude of the dose and the period of time over which it was administered.

Complications: Various manifestations of a hemorrhagic tendency made their appearance in eight of the twenty patients in this series. They were as follows: Purpura 4; sublingual ecchymosis 3; conjunctival hemorrhage 3; gingival hemorrhage 4; epistaxis 2; hematuria 3; spontaneous bleeding at wound site 3; vertigo 2; hematemesis 4; weakness and lassitude 7. There were variations in extent, intensity and duration of these signs and symptoms.

Treatment of the hemorrhagic tendency: Two patients received only supportive therapy, in order to evaluate the efficacy of the various therapeutic agents employed. Five patients received daily doses of 6.4 to 12.8 mg. of 2 methyl 1, -4 naphthohydroquinone 3 sodium sulfonate, and 300 mg. of cevitamic acid parenterally in addition to 150 mg. of nicotinic acid and the grated peel of four oranges daily by the oral route. One patient received only cevitamic acid, nicotinic acid and vitamin P in the above doses. Five patients received transfusions of 250-500 cc. of whole citrated blood.

*Effect of vitamins K, C, P and Nicotinic acid.*¹¹² Synthetic vitamin K substitute in doses substantially greater than those proven to be therapeutically effective in hypoprothrombinemias due to other causes, were ineffective in lowering the prothrombin time or controlling hemorrhage produced by the administration of the dicoumarin. A further report on the effect of vitamin K substitutes on the hypoprothrombinemia induced by administration of a 3, 3' methylene-bis-(4-hydroxycoumarin) will be embodied in a paper now in preparation. Vitamins C and P and nicotinic acid likewise exerted no detectable influence on the hemorrhagic tendency.

Effect of Transfusion. In patients showing hemorrhagic complications transfusion produced varying results. In two instances four day old bank blood was found to be ineffectual in the control of hemorrhage. Transfusion with fresh whole blood resulted in a fall in prothrombin time to a point below the hemorrhagic level, with complete cessation of hemorrhage in one case. Four other patients with hemorrhagic complications showed a temporary fall in prothrombin time with diminution in the severity of hemorrhages following transfusion. In these cases there was a subsequent prolongation of prothrombin time with recurrence of spontaneous hemorrhage requiring repetition of transfusion before control conditions were restored (cf. Table I).

TABLE II

INDICATING LACK OF RELATIONSHIP OF AGE, WEIGHT AND DOSE OF
DICOUMARIN TO HEMORRHAGIC COMPLICATIONS IN 20 PATIENTS

| HEMORRHAGIC GROUP | | | | | | NON-HEMORRHAGIC GROUP | | | | | |
|-------------------|---------|-------------|------------|-------|--------------------------|-----------------------|---------|-------------|------------|-------|--------------------------|
| Case No. | Age yr. | Body Wt. Kg | Total Dose | | Duration of Therapy Days | Case No. | Age yr. | Body Wt. Kg | Total Dose | | Duration of Therapy Days |
| | | | gm. | mg/kg | | | | | gm. | mg/kg | |
| 1 | 25 | 55.0 | 1.5 | 27.2 | 11 | 2 | 53 | 73.6 | 2.9 | 39.4 | 18 |
| 4 | 37 | 61.3 | 1.7 | 27.7 | 12 | 3 | 43 | 85.9 | 1.5 | 17.4 | 9 |
| 5 | 45 | 79.5 | 2.9 | 36.4 | 18 | 7 | 69 | 51.8 | 1.8 | 34.7 | 9 |
| 6 | 60 | 57.7 | 2.2 | 38.1 | 11 | 8 | 70 | 68.6 | .8 | 11.6 | 4 |
| 9 | 60 | 64.5 | 1.2 | 18.6 | 6 | 11 | 68 | 75.4 | 1.2 | 15.9 | 4 |
| 10 | 67 | 77.2 | 1.2 | 15.5 | 4 | 12 | 63 | 76.3 | .6 | 7.8 | 1 |
| 16 | 69 | 63.1 | 1.8 | 28.5 | 5 | 13 | 68 | 74.5 | 2.2 | 29.5 | 10 |
| 18 | 54 | 63.5 | 1.5 | 23.5 | 5 | 14 | 48 | 83.1 | 1.5 | 18.0 | 5 |
| | | | | | | 15 | 50 | 55.4 | 1.2 | 21.6 | 4 |
| | | | | | | 17 | 72 | 56.8 | 1.8 | 31.7 | 5 |
| | | | | | | 19 | 22 | 52.2 | 2.4 | 45.9 | 8 |
| | | | | | | 20 | 82 | 46.3 | 1.5 | 32.3 | 5 |

DISCUSSION

Dose: There was no apparent correlation between the incidence of hemorrhagic response and the amount of the drug administered (cf., Table II); moreover, comparable degrees of prothrombin- and coagulation-time prolongation were obtained in both bleeding and non-bleeding patients. As would be expected, the period over which the prothrombin time was prolonged was greater in those patients who received the larger doses. Hemorrhagic complications of equal intensity, equally resistant to therapy were noted in patient No. 5 (Wt. 79.5 Kg.) who had received 36.4 mg./Kg. of the dicoumarin and in patient No. 9 (Wt. 64.5 Kg.) who had received only 18.6 mg./Kg.

In patient No. 5, the bleeding tendency was of five days duration, and responded to two transfusions. In patient No. 9, hemorrhagic signs and symptoms persisted over a ten day period, requiring three transfusions for adequate control.

Link¹⁰⁹ and his associates have observed that response to dicoumarin in animals is enhanced by malnutrition, hepatic disorders, anacidity, dehydration, and abnormally high environmental temperature. Bearing in mind these factors, as possible contributory causes to the development of the hemorrhagic diathesis, a careful analysis of available laboratory and clinical data was made which yielded the following observations:

Temperature: During the course of our investigations the room temperature on the hospital wards was at times uncomfortably high, ranging from 80°-90°, although the average temperature during this period as recorded by the U.S. Weather Bureau was 74.7° F. Whether skin capillary dilatation associated with exposure to high environmental temperature, superadded to the widespread capillary relaxation noted by Bingham,¹⁰⁶ was a factor in the production of hemorrhagic manifestations has not yet been ascertained.

*Dehydration:*¹¹³⁻¹¹⁴ No evidence of dehydration was present in any of these patients prior to the onset of hemorrhage. Hematocrit, serum proteins, and plasma specific gravities were within normal range.

Anacidity: Gastric analysis in the patients who manifested the hemorrhagic diathesis revealed normal HCl concentration curves in four; hyperchlorhydria in one; and hypochlorhydria in three. Similar studies in non-bleeding patients showed normal HCl concentration curves in six, hypochlorhydria in three, and hyperchlorhydria in two patients.

Age: The age distribution of those patients, with and without hemorrhagic complications, was essentially the same (cf. Table II). Only three female patients were included in the series, hence no deductions regarding the influence of sex were warranted.

Nutritional status as estimated by weight and height tables was good in all but three patients. None of these showed hemorrhagic tendencies.

Capillary fragility: No apparent relationship between hemorrhagic tendency and capillary permeability could be established on the basis of the test used. There was no increase in capillary permeability over control determinations at the time of hemorrhage. Seven of the twenty patients showed abnormal capillary fragility prior to the administration of the dicoumarin. Of this group only two developed hemorrhagic complications which were not associated with a further increase in capillary fragility.

Sedimentation rate remained at control level throughout the period

of investigation in the non-hemorrhagic group. In those patients showing the hemorrhagic tendency an elevation of sedimentation rate occurred with the onset of hemorrhage, persisting until the hemorrhagic tendency subsided, at which time a slow return to control level was observed.

Renal function: Because of the inability of many of our patients to cooperate, studies of renal function by means of the urea clearance test were incomplete. Mosenthal¹¹⁷ renal concentration tests showed low fixed specific gravity in four patients of the hemorrhagic group, as contrasted with one patient in the group who showed no complications.

Hepatic function: Two patients showed significant bromsulphalein retention after 1 hour. One of these (patient No. 19) showed hemorrhagic signs; the other (patient No. 11) did not. The cephalin flocculation test was positive in two non-hemorrhagic patients and in one patient who exhibited the bleeding tendency.

From the foregoing it is difficult to attribute the hemorrhagic complications observed in this group of patients to any single factor.

The interval of twenty-four to seventy-two hours which transpires before the initial effect of the dicoumarin is observed would seem to suggest that a comparable interval is required for the dicoumarin to be converted into a prothrombin inhibitor, or to exert a direct effect upon the prothrombin-producing function of the liver. Bingham, Meyer and Pohle¹⁰⁶ reported a similar delayed action with intravenous administration. This demonstrates that the lag is not due to retarded absorption. It cannot be stated at this time whether the site of action of dicoumarin is in the liver or not.

The fact that in vitro studies have shown that the dicoumarin, as such, has no anti-coagulant activity would tend to minimize the importance of renal retention as a probable cause of the hemorrhagic diathesis. Undoubtedly, dose-level influences the tendency to hemorrhagic complications, since other observers who administered smaller or only single doses to patients reported no such manifestations. However, in addition to this, a combination of factors which for want of adequate evidence must be termed individual susceptibility, varying from patient to patient, would seem to be an important determinant in the production of the hemorrhagic tendency.

The conclusions drawn from this study are as follows:

1. In man, the oral administration of dicoumarin will prolong proth-

TABLE III

CONTRASTING CHARACTERISTICS OF DICOUMARIN AND HEPARIN

| Chemical Classification | <i>Dicoumarin</i> | <i>Heparin</i> |
|------------------------------------|--|---|
| | 3, 3'-Methylene-Bis-(4-Hydroxycoumarin) | Mucoitin polysulfuric acid |
| Preparation | 1. Extraction from spoiled sweet clover hay 2. Synthesis | Extraction from blood, liver, lung and other tissues Commercially it is prepared from lung and liver |
| Effect Manifested by | 1. Prolongation of prothrombin and coagulation times | 1. Inhibition of platelet agglutination 2. Prolongation of coagulation time |
| Effect Antagonized by | 1. Fresh whole blood | 1. Trypsin 2. Thrombokinase 3. Snake venom 4. Salmine sulfuric acid |
| Dose | Variable (approximately 300 mg. on alternate days in recent cases has proved satisfactory) | Variable (approximately 20 mg./Kg.) |
| Method of Administration | 1. Oral 2. Intravenous | Intravenous { Continuous Drip Multiple Divided Dose |
| Initial Response Occurs | 24-72 hours | Immediately |
| Duration of Effect | 2-26 days average 11.2 days | 1-4 hours |
| Hemorrhagic Manifestations | Purpura, Ecchymoses, Hematuria, Gingival hemorrhage, Epistaxis, Conjunctival hemorrhage | Hematomata, Hematuria, Cerebral hemorrhage |
| Hemorrhagic Tendency Controlled by | Transfusions of fresh whole blood or plasma | 1. Salmine sulfuric acid 2. Blood transfusion |

rombin and coagulation time.

2. Wide variations in degree and extent of response were observed in different patients.

3. Hemorrhagic reactions, resembling sweet clover disease in animals, occurred following the oral administration of dicoumarin in eight patients.

4. Evidence suggests that differences in individual susceptibility may be responsible in part for these hemorrhagic responses.

The contrasting characteristics of these two in vivo anti-coagulants—heparin and dicoumarin—are presented in Table III.

An attempt has been made to summarize the present status of the use of in-vivo anti-coagulants. Of these, heparin and the dicoumarin 3, 3' methylene-bis-(4-hydroxycoumarin) appear to be the most important and the most promising. They should be considered merely as steps toward our understanding of the factors and mechanisms involved in the important process of the coagulation of the blood. Some therapeutic indications have been outlined.

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STUDIES ON EXPERIMENTAL HYPERTENSION

XVIII. *Experimental Observations on the Humoral Mechanism of Hypertension**

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THE finding that persistent hypertension may be induced in the dog by constriction of both main renal arteries or by constriction of one main renal artery and extirpation of the contralateral kidney¹ has been fully confirmed by many investigators.²⁻⁸ Hypertension has now been produced by the same method in the monkey,⁹ rat,¹⁰⁻¹³ rabbit,^{14,15} goat and sheep.¹⁶ The development of this method was based upon the assumption that in the most common type of human hypertension in which fairly widespread vascular disease is almost an invariable accompaniment, the arterio- and arteriolosclerosis of the kidney is the primary condition which, in some way, determines the elevation of the blood pressure. Whatever may be the nature of the actual disturbance of hemodynamics which occurs in the human kidney the seat of arterio- and arteriolosclerosis, a similar effect on intrarenal hemodynamics is probably produced in animals by persistent constriction of the main renal artery. The resultant experimental hypertension is strong indication that in man too, the elevation of the blood pressure may be due to the renal vascular disease or any other kind of renal disease which might produce a similar effect on the renal circulation.

The experimental production of a disease process in animals is of value to human medicine in direct proportion to the resultant contribution to the elucidation of the cause and possible cure of its human counterpart. The various studies of experimental renal hypertension produced by constriction of the main renal artery have already brought out

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TABLE I

| <i>Subject</i> | <i>Human Essential Hypertension</i> | <i>Experimental Renal Hypertension</i> |
|--|--|--|
| Cardiac rate | Normal | Normal |
| Cardiac output | Normal ¹⁷⁻¹⁹ | Normal ²⁰ |
| Blood volume | Normal ^{21, 22} | Normal ^{23, 24} |
| Viscosity | Normal ²⁵ | Normal ²⁶ |
| Peripheral blood flow | Normal ^{27, 28*} | Normal ²⁹ |
| Sympathectomy | Does not abolish hypertension ²⁷ | Does not prevent or abolish hypertension ^{7, 23, 62, 63} |
| Resection of splanchnic nerves | Does not abolish hypertension ³⁰ | Does not prevent or abolish hypertension ³¹ |
| Renal blood flow | Apparently reduced ^{32, 33} | Reduced ^{34**} |
| Renal excretory function | (a) Benign phase normal ^{35, 36} (b) Malignant phase reduced ⁵³ | Benign phase normal ^{1, 3, 5, 6, 24, 37} Malignant phase reduced ³⁹ |
| Cardiac hypertrophy | Left ventricle when uncomplicated by failure ⁴⁰ | Left ventricle. Rat, ^{41, 42} Rabbit, ¹⁵ Dog ^{3, 24} |
| Pulmonary arterial pressure | Not altered when hypertension is uncomplicated by left heart failure, as indicated by normal right heart ³⁶ | Unaltered ⁴³ |
| Unilateral renal disease associated with hypertension | Cured by nephrectomy when proved unilateral ⁴⁴ | Cured by nephrectomy ^{1, 5, 6, 45} |
| Bilateral nephrectomy | No rise of pressure ⁴⁶ | No, rise of pressure ^{7, 47-50} |
| Thyroidectomy | Does not prevent or cure hypertension unless of the type associated with disease of the thyroid ⁵¹ | Does not prevent or abolish hypertension ⁵² |
| Generalized arteriolar necrosis and necrotizing arteriolitis | In malignant phase only ^{38, 53, 54} | In malignant phase only ⁵⁵⁻⁵⁷ |

* Controversial: Abramson, D. I. and Fierst, S. M.: Resting blood flow and peripheral vascular responses in hypertensive subjects, *Am. Heart J.*, 1942, 23:84.

** Controversial: Corcoran, A. C. and Page, I. H.: Renal aspects of experimental and clinical hypertension, *J. Lab. & Clin. Med.*, 1941, 26:1713.

clearly the many similarities of this type to human so-called "essential" hypertension which is so frequently associated with vascular disease, especially involving the kidneys. These similarities are briefly summarized in Table I.

The presence of fairly widespread arteriolosclerosis in cases of persistent benign human hypertension and the absence of this type of change in the arterioles of dogs in the benign phase of persistent experimental renal hypertension for as long as six years, as well as the finding of medial hypertrophy in the small arteries and arterioles in both human and experimental benign hypertension, merely emphasize the probability that in man the arteriolosclerosis precedes and is not caused by the hypertension. Thus, there is adequate indication that experimental renal hypertension and human 'essential hypertension' are closely similar, if not identical, and that results obtained in studies of pathogenesis, prevention or cure of the one may be directly applied to the other.

Much evidence has now accumulated which, both directly and indirectly, shows that the elevation of blood pressure which follows constriction of the main renal arteries is due to a humoral mechanism of renal origin. It has been shown, for example, that renal denervation,^{2, 4, 6, 7, 58} bilateral supradiaphragmatic excision of splanchnic nerves and lower four thoracic sympathetic ganglia,³¹ subdiaphragmatic splanchnicectomy with excision of celiac and upper lumbar ganglia,⁶ bilateral section of anterior nerve roots from 6th dorsal to 2nd lumbar inclusive,⁵⁹ destruction of the spinal cord^{60, 61} and complete sympathectomy, including denervation of heart,^{7, 23, 62, 63} neither prevent nor abolish the hypertension which results from constriction of the main renal arteries. The results of these studies eliminate a nervous reflex from the kidneys as the cause of the hypertension and indicate the probable implication of a humoral mechanism.

One of the direct indications that a humoral mechanism is involved in the pathogenesis of experimental renal hypertension is the finding⁶⁴ that if the renal veins are obstructed at the same time that the renal arteries are constricted, no rise of blood pressure occurs. Another piece of evidence is the finding that when a kidney is transplanted to the neck⁶ or groin,^{65, 66} with no nervous connections with the rest of the body, a rise of blood pressure still occurs when the main artery to the kidney is constricted. Similarly, the demonstration,⁶⁷⁻⁶⁹ that transplantation of an ischemic kidney from one dog to the neck of a nephrectom-

ized recipient causes an immediate and sustained rise of blood pressure as soon as blood is allowed to flow through the anastomosed vessels, indicates that some substance is washed from the kidney into the systemic circulation. Finally, the actual demonstration that the blood from a kidney with its main artery constricted is actively vasoconstrictor and pressor, whether this constriction is acute or chronic, is proof of the existence of a humoral mechanism.^{7,8,70-78}

That renal excretory function remains normal in benign experimental renal hypertension^{1,3,5,24} indicates that retention of nitrogenous metabolites is not a causative factor. The observation that bilateral nephrectomy, which results in azotemia, causes no elevation of blood pressure^{7,48-50} is additional proof that retention of nitrogenous metabolites plays no part in the pathogenesis of the hypertension but indicates clearly that the presence of the kidneys in the body is a necessary condition for the elevation of the blood pressure.

THE HUMORAL MECHANISM

The early studies on the pathogenesis of experimental renal hypertension led directly to a renewal of interest in some old observations made in 1898 by Tigerstedt and Bergman⁷⁹ who found that a saline extract of rabbit kidneys had a prolonged pressor effect when injected into another rabbit. They named the active ingredient of the renal extract "Renin." In recent years, especially since the production of experimental renal hypertension, all of the findings of Tigerstedt and Bergman have been confirmed and extended by a large number of investigations which have dealt with the preparation, purification, properties and mode of action of the renal extract which is capable of producing an elevation of blood pressure when it is injected intravenously and for which the term renin has been generally adopted.^{50,80-105}

Renin:

Tigerstedt and Bergman found that renin was a protein, not dialyzable and destroyed by heat. They further found that it had a greater and more prolonged pressor effect when injected into a bilaterally nephrectomized animal, and that when renin was injected repeatedly, with intervals of only a few minutes between injections, it elicited decreasing responses of the blood pressure and eventually no response. This pheno-

menon they referred to as tachyphylaxis. Since they found that section of the spinal cord did not affect the pressor response to an intravenous injection of renin, and that renin had no effect on the isolated perfused heart, they concluded that its effect was exerted directly on the peripheral blood vessels.

In the more recent investigations these findings of Tigerstedt and Bergman have been confirmed. The results of further studies on the behavior of renin when it is subjected to ammonium sulfate precipitation and dialysis^{85,94,96} suggest that it is a pseudoglobulin, but this cannot be accepted as final until it has been purified and studied by the method of electrodialysis. It has also been found¹⁰⁵ that in an electric field renin migrates to the cathode and that the isoelectric point of renin lies between a pH of 6.5 to 7.5.

Renin has not yet been isolated in pure form but various methods of extraction and purification have been published,^{87,91,94,96,101,104} and it has been shown that the purest product so far produced is different from the known sympathicomimetic amines in that its action is not potentiated by cocaine⁹² or reversed by ergotamine^{93,94,96} or by piperidomethyl-3-benzodioxane.^{106,107} It has also been shown that the action of renin differs from that of adrenalin, pituitrin, and tyramine in that the pressor response to an intravenous injection of renin is not associated with a decrease in peripheral blood flow or fall of skin temperature.^{86,97}

Out of the early recent studies of the physiological properties of renin came the discovery that renin is not effective unless injected intravenously and that it has no vasoconstrictor properties when added to Ringer's solution which is being perfused through an isolated organ. It is, therefore, not directly a pressor substance. This was a stumbling block to the proper understanding of the mechanism of the pressor effect of renin when injected intravenously. A study by Friedman, Abramson and Marx⁹² indicated the answer to this problem, for they found that when Tyrode's solution was used for the perfusion of the isolated dog's tail no vasoconstriction occurred when renin was added, but that when blood plasma was used as the perfusing fluid the addition of renin did produce marked vasoconstriction. This observation was followed by the independent and coincidental finding by Page and collaborators^{108,109} and by a group of South American workers^{99,100,110} that the interaction of renin and blood plasma or serum in

vitro results in the formation of a new substance which is an effective vasoconstrictor and therefore a pressor substance. Page and collaborators gave the name "renin-activator" to the substance in the blood which interacts with renin and called the resultant vasoconstrictor and pressor substance "angiotonin".¹¹¹ The South American workers named the substance in the blood "hypertensin precursor" and the vasoconstrictor and pressor substance "hypertensin".⁹⁹

It is of interest to note here some observations first reported by Dicker¹¹² and confirmed by Taquini,^{113,114} that when the main renal artery or the entire renal pedicle was occluded for varying periods of time, there was a prompt and prolonged rise of arterial blood pressure after the restoration of the renal circulation by release of the renal artery or renal pedicle. This contribution has been fully corroborated by other investigators.¹¹⁵⁻¹¹⁹ Taquini¹¹³ also showed that if such a completely ischemic dog's kidney was removed and the clamp on the pedicle not released until the renal vessels were anastomosed to the carotid artery and jugular vein of a nephrectomized recipient, there was a marked rise in the blood pressure of the recipient when the circulation in the completely ischemic kidney was reestablished. This same effect was observed from the same procedure with partially ischemic kidneys from dogs with chronic renal hypertension. The result indicated that a humoral mechanism, probably identical, was involved in both cases. The study of acute, complete renal ischemia was carried further by Prinzmetal and collaborators^{107,118} who demonstrated that renin was the agent present in the saline perfusates of such kidneys, and that the rise in systemic blood pressure which followed the release of the pedicle was therefore due to the liberation of renin into the general circulation. These findings have been recently confirmed.^{120,121} Taquini and Braun-Menendez¹²⁰ even demonstrated renin in the systemic arterial blood of animals following release of the pedicle of completely ischemic kidneys.

The discovery that renin is not by itself a vasoconstrictor substance and the subsequent finding that it needs a substrate in the blood stream with which to produce a pressor substance has thrown light on the hitherto obscure phenomenon of tachyphylaxis. Page and co-workers⁹³ showed that the reason for the progressive decrease in the response to consecutive injections of renin was due to exhaustion of renin-activator in the blood. This was confirmed by the South Americans⁹⁹ who found in addition that there is an excess of renin circulating in the blood stream

of tachyphylactic animals which, along with the absence of hypertensin precursor adequately explains the reason for failure to respond to further injections of the same substance.

It has also been shown that the action of renin is not affected by hypophysectomy, thyroidectomy, pancreatectomy, gonadectomy, splenectomy, abdominal evisceration, or destruction of the spinal cord.^{89,92} It is known, however, that bilateral adrenalectomy is followed by progressive decrease in the response to injections of renin.¹²²⁻¹²⁴ The full significance of this latter finding is not yet completely elucidated. It will be referred to briefly again later in this paper.

It was first noted by Tigerstedt and Bergman that in bilaterally nephrectomized animals renin has a more prolonged and striking pressor effect and that tachyphylaxis is less pronounced in such animals. This has been explained by Page¹⁰⁰ and confirmed by the South American investigators⁹⁹ as due to an increase in the amount of renin-activator circulating in the blood stream of such "arenal" animals.

The indications that renin may be the agent which initiates the rise of arterial blood pressure following constriction of the main renal artery are further strengthened by correlating the actual effects of intravenously injected renin on various functions under various conditions with similar functions and conditions in animals with experimental renal hypertension. These are compared in Table II which shows that the physiological effects of renin, when injected intravenously into a normal animal, are identical with the observed hemodynamic state of animals hypertensive due to clamping of the main renal artery.

Even more direct evidence as to the role of renin in initiating the rise of blood pressure which follows constriction of the renal arteries is to be found in the demonstration that extracts of kidneys of animals with chronic renal hypertension^{139,140} and of kidneys with acute complete ischemia¹¹⁸ contain more renin than extracts of the opposite normal kidneys. Direct proof, however, that renin is concerned in the genesis of experimental renal hypertension is furnished by the demonstration of renin in renal vein blood and systemic blood of animals made hypertensive by constriction of the renal arteries.^{75,76,141}

Recent studies show that renin plays a part in the maintenance of blood pressure after severe hemorrhage and in shock.¹⁴¹⁻¹⁴⁶ Renin is liberated from the kidneys and can be demonstrated not only in renal vein blood but also in systemic blood.¹⁴¹ The liberation of the renin in these

TABLE II

| <i>Organ or Condition Studied</i> | <i>Effect of Intravenous Injection of Renin in Normal Animals</i> | <i>Parallel in Experimental Renal Hypertension</i> |
|-----------------------------------|--|---|
| Heart Rate | Unaltered from normal. ^{79, 92, 98} | Unaltered from normal. ²⁰ |
| Cardiac Output | Unaltered from normal. ^{88, 125} | Unaltered from normal. ²⁰ |
| Complete Sympathectomy | Does not reduce B.P. rise due to renin. ¹²⁶ | Does not reduce B.P. rise in experimental renal hypertension. ^{7, 23, 62, 63} |
| Pithing | Does not reduce B.P. rise due to renin. ^{79, 92, 93} | Does not abolish experimental renal hypertension. ^{60, 61} |
| Hypophysectomy | Does not reduce B.P. rise due to renin. ^{109, 122, 127} | Does not prevent or abolish experimental renal hypertension. ^{123, 129} |
| Thyroidectomy | Does not reduce B.P. rise due to renin. ¹²⁷ | Does not prevent or abolish experimental renal hypertension. ⁵² |
| Gonadectomy | Does not reduce B.P. rise due to renin. ¹²² | Does not prevent or abolish experimental renal hypertension. ¹³⁰ |
| Acute Adrenalectomy | Does not reduce B.P. rise due to renin. ⁹³ | Does not reduce rise of B.P. when ischemic kidney of hypertensive dog is grafted into neck of normal dog. ¹³¹ |
| Chronic Adrenalectomy | Abolishes B.P. response to renin. ^{122, 123, 124} Response restored by adrenal cortical extract or D.C.S. ¹²⁴ | Prevents or abolishes experimental renal hypertension. ^{1, 6, 39, 130, 132} Hypertension maintained in adrenalectomized dogs treated with adrenal cortical extract or D.C.S. ³⁹ |
| Bilateral Nephrectomy | Response to renin greater. ^{79, 127, 133, 134, 135} | Response to grafting of ischemic kidney of hypertensive dog greater in nephrectomized than normal recipient. ⁸ |
| Peripheral Blood flow | No decrease during rise of B.P. due to renin. ⁸⁶ | No decrease in hypertensive rabbits with renal ischemia. ²⁹ |
| Renal Hemodynamics | Direct evidence shows decrease of renal blood flow. ^{89, 92, 136} Indirect evidence of efferent arteriolar constriction. ⁸⁹ | Direct evidence shows decrease of renal blood flow. ³⁴ Indirect evidence of efferent arteriolar constriction. ¹⁵⁹ |
| Blood Pressure | Infusion of renin causes persistent elevation. ¹³⁷ Rise not reversed by 933F. ^{106, 107} Repeated injections cause tachyphylaxis. ^{79, 92, 93, 99} Renin causes no rise in pulmonary arterial pressure. ¹³⁸ | Constriction of renal arteries causes persistent elevation. ¹ The rise of B.P. due to release of the pedicle of a completely ischemic cat kidney is not reversed by 933F. ^{107, 118} If a cat is first rendered tachyphylactic to renin, release of pedicle of completely ischemic kidney is not followed by usual rise of B.P. ^{118, 121} No rise of pulmonary arterial pressure in experimental renal hypertension. ⁴³ |

D.C.S. = Desoxycorticosterone acetate.

B.P. = Blood pressure.

circumstances is presumably due to the hemodynamic disturbance which is caused by the fall of blood pressure and which simulates that caused by constriction of the renal arteries.

THE SUBSTRATE OF RENIN [RENIN-ACTIVATOR (PREANGIOTONIN) OR
HYPERTENSIN PRECURSOR (PREHYPERTENSIN)] AND THE
NATURE OF ITS REACTION WITH RENIN

The substance in the blood stream upon which renin acts was named renin-activator by Page and co-workers and hypertensin precursor or hypertensinogen by Braun-Menendez and his collaborators. If it is eventually proved that the resultant product of the interaction of these two substances is the cause of elevated blood pressure, then the specific term "hypertensin" of the South Americans will be more pertinent than the non-specific term "angiotonin." However, until the substance in question is actually isolated from the systemic circulation of patients with essential hypertension and/or animals with experimental renal hypertension, it is well to continue to use both terminologies side by side, but to bring them in line we suggest the terms "preangiotonin" for renin-activator and "prehypertensin" for hypertensin precursor, which will be used in the remainder of this paper.

Both Page and co-workers and Braun-Menendez and his co-workers agree upon the identity and the properties of renin-activator (preangiotonin) or hypertensin precursor (prehypertensin). It has been found to be a protein, in all probability a pseudoglobulin rather than a euglobulin, since it is soluble in distilled water and is precipitated from blood serum between 0.34 and 0.6 saturation with ammonium sulfate, findings which have been confirmed in our laboratory by Dr. Yale J. Katz. It is heat labile, non-dialyzable and not ultrafiltrable and is present in blood serum and red blood cells.^{99,109} It is undiminished following hyophysectomy¹⁰⁹ but we have found that it decreases and finally almost disappears from the systemic blood of untreated adrenalectomized male dogs. Adequate therapy with adrenal cortical hormones or desoxycorticosterone acetate results in a return of preangiotonin (prehypertensin) to the normal level. We have also found that it disappears from the blood as the result of destruction of the liver. Full details of these studies will be given in a forthcoming publication on the role of the adrenal glands in experimental renal hypertension. Page failed to find any effect on renin-activator (preangiotonin) as the result of bilateral adrenalectomy, but

he has recently reported that it disappears from the blood when the liver is removed or severely damaged by a hepatotoxic substance.¹⁴⁷

It has been further found both by Page and collaborators, and the South American workers that renin-activator (hypertensin precursor) is increased in the serum of the bilaterally nephrectomized dog^{93,99} and exhausted in renin tachyphylaxis. In addition, renin-activator has been reported as increased in experimental renal hypertension and human essential hypertension.^{99,148,149}

The South Americans have found, in addition, that the reaction between renin and hypertensin precursor (prehypertensin) is rather specific in that the effect of renin on the substrate in the blood could not be reproduced by other enzymes such as pepsin, pancreatin, papain or extracts of liver or spleen. They also found that hypertensin precursor (prehypertensin) was present only in blood globulins and that the latter could not be replaced by hemoglobin, casein, milk, egg or blood albumin, or by liver, spleen, thymus, testes, lung, heart, skeletal muscle or vegetable proteins.⁹⁹

Subsequent studies with pepsin, however, by Croxatto and Croxatto¹⁵⁰ have shown that pepsin will produce a vasoconstrictor substance when it is allowed to act on blood globulins. They showed that the pressor substance produced by the action of pepsin was identical in its behavior to hypertensin (angiotonin) insofar as this could be chemically and pharmacologically determined. This has recently been confirmed by Helmer and Page¹⁵¹ and by Dr. Yale J. Katz in our laboratory.

Interesting studies on the specificity of renin and its substrate in the blood have been made in a variety of different species by the group of South American workers^{152,153} by Corcoran, Helmer and Page¹⁵⁴ and others.^{134,155-157} These observations have been conducted on man, baboon, monkey, cow, sheep, horse, pig, dog, cat, rabbit, rat, dolphin, chicken, duck, snake, shark, toad, aglomerular fish, carp and catfish. The results of these studies are best summarized in Table III.

As to the reaction between renin and preangiotonin (prehypertensin), this seems to be enzymatic,¹⁵⁸ as is indicated by the following known properties of these participants and the characteristics of the reaction itself:

1. Renin is a protein, most probably a pseudoglobulin.
2. Renin is non-dialyzable and thermolabile (destroyed above 56°C^{94}).

TABLE III

*Renin, from
the kidney of:*

*Substrate, in
the blood of:*

| | | |
|-------------------|--|-------------------|
| Man | } Will react with any of these | Man |
| Baboon | | Baboon |
| Monkey | | Monkey |
| Cow | } Will react with all yet tested | Cow |
| Horse | | Horse |
| Pig | | Pig |
| Sheep | | Sheep |
| Dog | } Each will react with any of these, but not with human, baboon or monkey substrate | Dog |
| Cat | | Cat |
| Rabbit | | Rabbit |
| Rat | | Rat |
| Dolphin | | Dolphin |
| Carp | | Carp |
| Catfish | | Catfish |
| Chicken | } Each reacts with own substrate | Chicken |
| Duck | | Duck |
| Snake | } No demonstrable homologous or heterologous interactions; therefore no renin or substrate | Snake |
| Toad | | Toad |
| Agglomerular fish | | Agglomerular fish |

To produce angiotonin (hypertensin), which causes vasoconstriction, or gives a pressor response, in every one of these species yet tested, including the poikilotherms.

3. Only a small amount of renin is necessary in proportion to the amount of blood substrate, and the amount of angiotonin (hypertensin) formed is proportional to the amount of blood globulins.
4. The reaction is affected by temperature; hastened by incubation at 37° C. and retarded or stopped at 0° C.
5. The substrate in the blood is also a protein, non-dialyzable and thermolabile.^{99,109}
6. The end product of the reaction, angiotonin (hypertensin), is dialyzable and thermostabile, which indicates that the reaction is disintegrative rather than integrative, as is implied by Page's assertion that renin must be "activated."
7. The fact that renin, evidently a proteolytic enzyme, may be actually replaced by pepsin, a known proteolytic enzyme, is further proof of a disintegrative reaction. It may be that renin differs primarily from pepsin in that it acts at the natural pH of the blood and not in the pH range of pepsin activity, while pepsin cannot produce a pressor substance from blood globulins in the pH range of renin activity.

It is for these reasons that we consider renin an enzyme and preangiotonin (prehypertensin) its substrate. Page¹⁵⁹ agrees that this is now his working hypothesis.

ANGIOTONIN (HYPERTENSIN)

The substance formed by the action of renin on preangiotonin (prehypertensin) is the final effector vasoconstrictor and pressor substance of the humoral mechanism. It was independently discovered both by Page and co-workers, who named it angiotonin, and by the South American investigators, who named it hypertensin.

Page and Helmer¹¹¹ have reported the crystallization of angiotonin in the form of the picrate and oxalate, but not in uncombined pure form, and as yet have not published the melting point of any of these crystals or the probable structure of pure angiotonin. Considerable information is available, however, about the properties of this pressor substance. It is heat and acid stabile, water and alcohol soluble, fluorescent, alkali labile and gives the color reaction for arginine. Its pressor effect is immediate, the maximum rise abrupt, and the entire period of elevation of blood pressure brief, more like the pressor effect of epine-

phrine than that of renin. Renin gives a slow, maximum rise followed by a sustained elevation which may last thirty minutes or longer before returning to normal. This prolonged action of renin is assumed to be caused by the continuous liberation of angiotonin (hypertensin) due to the interaction of renin and preangiotonin (prehypertensin) in the blood stream. Page claims that angiotonin, like renin, also induces tachyphylaxis, and that "it needs its own activator", which he calls angiotonin-activator. He also found that renin destroys angiotonin when incubated with it. In addition, the pressor response to angiotonin was found to be unaffected by cocaine or atropine, or by pithing or adrenalectomy.¹¹¹ Other studies showed that the pressor response to angiotonin is greatly increased in nephrectomized dogs and that angiotonin, unlike renin, causes vasoconstriction when perfused with Ringer's solution through an isolated organ.¹³³ Later studies proved conclusively that the indirect effect of renin and the direct action of angiotonin are exerted on the peripheral blood vessels.¹⁶⁰

The South Americans confirmed almost all of Page's findings with regard to hypertensin (angiotonin) but could not demonstrate tachyphylaxis to this substance. They also found that it produced a direct vasoconstrictor action, that its action was not reversed by piperidomethyl-3-benzodioxane (933F) and not affected by vagotomy or by excision of the carotid bodies, splanchnic nerves, liver, or adrenals, by evisceration or by destruction of the medulla.¹⁶¹ They found that it was dialyzable, soluble in glacial acetic acid, liquid phenol and ethylene glycol, and that it was destroyed by pepsin.⁹⁹ Destruction by pepsin indicates that hypertensin (angiotonin) may be a polypeptide, although Page and Helmer¹¹¹ claim a negative biuret for angiotonin. Braun-Mendez and co-workers¹⁰⁰ also found that hypertensin was destroyed by trypsin and extracts of liver and spleen as well as by fresh normal blood serum, and that this ability of fresh serum to destroy hypertensin was decreased following bilateral nephrectomy. This substance which destroys hypertensin has been named hypertensinase by the South Americans.^{99,162}

Many studies have now been reported on the physiological effects of angiotonin on the blood pressure, heart rate and output, coronary blood flow, venous pressure, viscera and renal blood flow and clearance.¹⁶³⁻¹⁷⁵ In general, these correspond to the effects of the intravenous injection of renin in intact animals. Any differences that have been

found between the effects of intravenously injected renin and angiotonin may be due to the fact that the angiotonin formed from renin in vivo differs in some respects from the angiotonin produced in vitro.

The Evidence for the Existence of "Angiotonin-Activator". Page has stated,¹⁷⁶ "Since renin requires a second substance in order for it to exhibit pressor action, it follows that there is some reaction between these two substance to produce a third." Although Page demonstrated that renin and renin-activator form a new substance, angiotonin, yet he failed even to postulate the existence of a second new substance as the reaction product of angiotonin and angiotonin-activator.

In reference to angiotonin Page also stated,¹³³ "It does not appear to be the end product of the reaction between renin and renin-activator, for it itself is destroyed by further contact with renin." This statement was invalidated by the work of the South Americans,¹⁶² who showed that another enzyme contained in renal extract, which they named hypertensinase, was responsible for the destruction of angiotonin (hypertensin) and that highly purified renin does not do it. These findings we have verified. They indicate that angiotonin (hypertensin) is the end product of the reaction between renin and renin-activator and thus further indicate that there is no need for angiotonin-activator.

In regard to the question of angiotonin tachyphylaxis, which Page observed and which he blamed partially on the exhaustion of angiotonin-activator, the South Americans⁹⁹ do not find this phenomenon in intact animals, nor do we. The South Americans and ourselves used the natural form of angiotonin produced by incubation of renin with serum. The difference in results may be due to the use of crystalline salts of angiotonin by Page and collaborators.

Again in reference to angiotonin-activator, Page said¹³³ "We employ the name, as in the case of renin-activator, to connote that neither renin nor angiotonin exerts a pressor action in the absence of their respective activators." It is of interest in this connection to note that angiotonin (hypertensin) will cause vasoconstriction in all species so far tested, including poikilotherms. Every species, from the kidneys of which renin has been extracted, whether this renin was effective in the same or in other species, has been found also to possess prehypertensin (preangiotonin) in its own blood. The renal extract of toad and snake,¹⁵³ prepared by the method used for the extraction of renin, is not effective

in the toad, snake or any other species. Thus the toad and snake contain no demonstrable renin or prehypertensin. Yet hypertensin (angiotonin) is effective in raising the blood pressure in both snake and toad.¹⁵³ It seems far fetched, therefore, to assume the existence of "angiotonin-activator" in animals which do not possess any of the other elements of the humoral mechanism of hypertension, yet give a definite vasoconstrictor and pressor response to the injection of angiotonin.

The difficulty of correctly ascertaining just what function Page assigns to "angiotonin-activator" or what its place in the humoral mechanism is, may well be gathered from his recent statements that "Angiotonin may be an intermediate in a series of reactions which ultimately lead to its destruction, i.e., renin + renin-activator \rightarrow angiotonin + angiotonin-activator \rightarrow vaso-inactive substance,"¹⁵⁹ and "It is my guess that angiotonin is only one in a series of substances, although probably a key substance which are formed when renin is allowed to act."¹⁷⁶

It may be stated, therefore, that further evidence is needed for the existence of angiotonin-activator, and that even the demonstration of angiotonin tachyphylaxis¹⁷⁵ in isolated organs must be differentiated from a possible inhibitory toxic or other effect of the injected material on the blood vessels.

HYPERTENSINASE (ANGIOTONINASE)

Early in the course of their studies on the humoral mechanism the South Americans discovered that normal blood serum would destroy hypertensin in vitro, and they advanced the name "hypertensinase" for the responsible destructive agent. They demonstrated that hypertensinase, which was destroyed by heat (60° C.) could be separated from renin and prehypertensin, both of which are also heat labile, by incubating at 37° C. at a pH of 3.9 for fifteen minutes. Thus they showed that if the hypertensinase in renin and serum were first destroyed by this method, which leaves renin and prehypertensin unaltered, prolonged contact of renin and prehypertensin then resulted in a maximum yield of hypertensin which remained constant despite the length of incubation. The optimum pH of hypertensinase activity was found to be between 7.5 and 8.5, and its action to be affected by temperature, for at 0° C. its action stops. Thus they believe it to be an enzyme. It can be precipitated by half-saturation with ammonium sulfate, but not by dialysis.

In their study of the hypertensinase content of various tissues Fasciolo et al¹⁶² found that kidney cortex had 1500, intestinal mucosa 1200-1600, pancreas and spleen 200, hemolyzed red cells and liver 100 units per gram. Serum and plasma (without hemolysis) were found to have only about 1 unit per gram.

That the kidney may be the main source of the hypertensinase in normal blood is indicated by the finding that there is almost a complete disappearance of hypertensinase from the blood stream of bilaterally nephrectomized dogs.¹⁶²

Harrison, Grollman and Williams¹⁷⁷⁻¹⁷⁹ were the first to attempt the treatment of experimental renal hypertension with renal extracts, although they had made no in vitro studies of the action of these extracts on angiotonin (hypertensin). Their approach was based on the observations that the normal kidney, by some humoral means, might play a part in eliminating the hypertensive effect of a contralateral ischemic kidney, since the blood pressure of such an animal tends to return to normal, and also that when the normal kidney is removed, in the presence of the ischemic one, the blood pressure ascends to and remains at a much higher level.

The idea that the normal kidney might play a part in the elimination of the "chemical mediator" in experimental hypertension was, incidentally, studied by Katz and Rodbard,¹⁸⁰⁻¹⁸² who confirmed the fact that the blood pressure falls to normal in six hours after the removal of a single ischemic kidney⁶ and also observed that it takes five times as long for it to reach normal after removal of both kidneys when one or both were ischemic. They believed that the more rapid fall of the blood pressure to normal levels in the presence of normal kidney tissue, as contrasted with the slow fall in its absence, might be due to the excretion or in vivo destruction of the "chemical mediator" by the remaining normal kidney. By constructing a uretero-venous fistula on the side of the normal kidney they showed that removal of the opposite ischemic kidney was still followed by a rapid, six hour fall of the blood pressure to normal, and concluded that the normal renal tissue destroyed the "chemical mediator," since its excretion back into the blood stream would have kept the blood pressure elevated for a length of time comparable to that necessary in the absence of any renal tissue.¹⁸² Since then, Dexter and Braun-Menendez¹⁸³ have demonstrated that the renal threshold of renin is too high for excretion of renin to account for the

stabilizing role of the normal kidney.

Independently of Harrison and collaborators, Page and his collaborators¹⁸⁴⁻¹⁸⁶ reported the treatment of hypertension with renal extracts containing angiotonin-inhibitor. The basis of their approach was different from that of the South Americans and of Harrison and co-workers, for they¹³³ had previously published their findings that renin and angiotonin tachyphylaxis were both due to more than simple exhaustion of renin-activator and angiotonin-activator, and had postulated the presence of renin-inhibitor and angiotonin-inhibitor. They believed that it was the loss of these two inhibitors after nephrectomy that accounted in large measure for the increased sensitivity of nephrectomized animals to renin and angiotonin. Although in their first publication they claimed that the blood of hypertensive animals treated with their renal extracts no longer contained renin-activator or angiotonin-activator,¹⁸⁴ neither this finding nor the existence of renin-inhibitor has been confirmed. All of their work was done *in vivo*, but recently they^{187,188} have confirmed the results of Fasciolo and collaborators¹⁶² on the ability of extracts of various organs to destroy angiotonin *in vitro*, which we have also confirmed.

Since the existence of a substance which destroys hypertensin (angiotonin) was first described by the South Americans and shown to be due to an enzyme which they named hypertensinase, we believe that to keep the terminologies similar, until a final one is adopted, the corresponding term angiotoninase is *apropos* for "angiotonin-inhibitor," for the action of the enzyme in question is not that of inhibition of angiotonin, or suppression of renin- or angiotonin-activator, but the actual destruction of angiotonin itself. Because of the inconsistency of their results, the South Americans¹⁴¹ did not publish the effect of treatment of experimental renal hypertension with renal extracts containing hypertensinase. Since it has not yet been shown that the possible anti-pressor effect of renal extracts of various kinds that have been used for the treatment of hypertension is actually due to hypertensinase (angiotoninase) it is well for the present to refer to such extracts as anti-pressor renal extracts.

Friedman¹⁶¹ demonstrated that renal vein blood from an ischemic dog's kidney contained much less hypertensinase than renal vein blood from normal kidneys. This throws light on the earlier experiments by Freeman¹⁸⁹ who found that normal dog's blood would reduce the blood

pressure of dogs hypertensive due to constriction of the main renal arteries, whereas blood from hypertensive dogs gave no such effect. In this case the antipressor effect may have been due to the presence of hypertensinase in normal blood and its diminution in the blood of hypertensive animals, just as other previously cited results in bilaterally nephrectomized animals may have been due to the absence of hypertensinase in this condition.

NON-SPECIFIC PRESSOR AND ANTI-PRESSOR SUBSTANCES

An indication of the part which the kidney might play in the elaboration of at least one of the substances involved in the humoral mechanism of hypertension has been given by a series of important studies by Bing and collaborators.¹⁹⁰⁻¹⁹³ They have demonstrated that an ischemic kidney is capable, by effecting decarboxylation, of converting l-dopa (l-dihydroxyphenylalanine), a substance with no pressor properties, into hydroxytyramine, a powerful pressor substance. The amount of hydroxytyramine formed in the kidney from dopa, only under conditions of oxygen lack, was found to be proportional to the reduction of blood flow through the perfused kidney.¹⁹¹ On the contrary, l-dopa added to normal blood being perfused through a kidney with normal blood flow was not converted into hydroxytyramine. It is of special significance that although liver and intestine also contain l-dopa-decarboxylase, yet these organs were unable, even when their circulation was reduced, to produce hydroxytyramine from dopa added to the blood. Similarly, it is only when the main renal artery is constricted that experimental hypertension results in the dog.^{194,195} In further experiments on artificially perfused kidneys, it was found that the ischemic human kidney also converted dopa to hydroxytyramine.¹⁹⁰ The above experiments were done with kidneys *in vitro*, but Bing was also able to show that partially or completely ischemic cat kidneys converted dopa into hydroxytyramine *in vivo*.¹⁹² As the result of these studies Bing has not concluded that hydroxytyramine is the cause of, or is in any way involved in, the pathogenesis of experimental renal hypertension, for he has demonstrated that angiotonin (hypertensin) is destroyed by a different fraction of renal extract than is hydroxytyramine, and that these two pressor substances are destroyed by different mechanisms.¹⁹³ This fact, along with his finding that renin was unable to effect decarboxylation of dopa and convert it to hydroxytyramine,¹⁹⁰ helps

to emphasize Bing's contention that he does not claim that hydroxytyramine is the cause of experimental renal hypertension. In this respect he has already been misquoted.¹⁹⁶ He has merely intended to show that when the blood flow to a kidney has been reduced the organ behaves differently than when the circulation is normal and that under these conditions it is capable of converting an amino acid, itself without pressor properties, into a powerful pressor amine.

Schroeder and Adams^{197,198} have found that tyrosinase, a phenolic oxidase, has the power to destroy angiotonin *in vitro*. In all of their tests in which tyrosinase alone was added to angiotonin, and the two shaken together, very little oxygen was absorbed and the angiotonin lost none of its pressor activity. When a small amount of blood serum, however, was added to the mixture of tyrosinase and angiotonin, oxygen was rapidly absorbed and the angiotonin was completely inactivated. Schroeder and Adams concluded that tyrosinase destroyed the angiotonin, but in the light of our present knowledge it is only fair to conclude that the effect may have been due to the hypertensinase in the blood serum and not to the tyrosinase itself. Nevertheless, Croxatto and Croxatto¹⁹⁹ found that tyrosinase from mushrooms and amine oxidase from the liver of the squid, did destroy the vasoconstrictor activity of hypertensin as tested by Laewen-Trendelenberg technique on the toad.

The presumable destruction of angiotonin by tyrosinase led Schroeder¹⁹⁸ to postulate that angiotonin, like adrenalin and tyramine, "may accordingly contain a phenolic group." On this basis he undertook the treatment of experimental and human hypertension with tyrosinase and found that it reduced the blood pressure. Martin and collaborators¹⁹⁶ also found that tyrosinase will lower the blood pressure of hypertensive dogs, but added that this effect of tyrosinase was greatly enhanced by the addition of catechol.* How these results are related to the antipressor effects of renal extracts in experimental renal and in human hypertension is far from clear. When it is realized that such substances as typhoid vaccine and sterile milk²⁰⁰ can also cause a reduction of blood pressure in experimental renal and human hypertension, the intricacy of this phase of the problem of hypertension becomes obvious. The present status of the treatment of experimental renal hypertension is reviewed in full in a forthcoming publication.²⁰⁰

* In a personal communication from Dr. Myron Prinzmetal²⁰¹ we have learned that a mushroom tyrosinase preparation, in which the tyrosinase was inactivated by heat, was also effective in producing a significant lowering of blood pressure and remission of other symptoms of human hypertension, when the extract was administered by intramuscular injection.

SUMMARY

It has been demonstrated that after constriction of the main renal arteries to a sufficient degree to produce experimental renal hypertension, renin, an enzyme, is liberated into renal vein blood. It has been shown that this enzyme, renin, interacts with preangiotonin (prehypertensin) a pseudoglobulin substrate in systemic blood, probably produced by the liver in the presence of an adequate amount of functioning adrenal cortical tissue, to form the final effector vasoconstrictor and pressor substance, angiotonin (hypertensin). It has also been demonstrated that the physiological effects of the intravenous injection of renin are identical to the hemodynamic alterations found in experimental renal hypertension and in human essential hypertension. It follows, therefore, that the humoral mechanism noted above may also be responsible for the elevation of blood pressure in human essential hypertension. Although the demonstration in hypertensive blood of vasoconstrictor substances which may possibly be related to this humoral mechanism, has been reported, the proof that angiotonin is the responsible agent, awaits its isolation from the systemic blood of human beings with hypertension.

In addition to renin, preangiotonin (prehypertensin) and angiotonin (hypertensin) which are involved in the humoral mechanism of experimental renal hypertension, a fourth factor, hypertensinase (angiotoninase) has been discovered. Although this substance, an enzyme, destroys angiotonin (hypertensin) in vitro, there is no proof yet available that it is effective in lowering blood pressure in man or animals with hypertension. It has not yet been shown that the anti-pressor renal extracts with which hypertension is said to have been lowered in man and animals are rich in hypertensinase and inactive when this enzyme is destroyed. The exact nature of the effective substance in anti-pressor renal extracts which have been used in the treatment of hypertension, remains to be elucidated.

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RECONSTITUTED MILK*

1. *Definition*

Reconstituted milk is a fluid resembling ordinary milk in appearance and taste; it is prepared from butterfat, dried skim milk and water by means of emulsifying apparatus. When prepared by exposure to temperatures of 150° F. or less, skim milk powder preserves its emulsifying qualities. Such low temperatures cannot be used in the process of drying whole milk since lipolytic enzymes are not destroyed at these temperatures and they react on the milk fats with a tendency to the development of rancidity. Temperatures above 175° F. are necessary to preserve the fat of dried whole milk in the powdered state. High temperatures coagulate the milk proteins and make them insoluble. The particles remain suspended in the water and the taste of the milk is objectionable. For this reason whole dried milk and evaporated milk are unsatisfactory as beverages. The term "reconstituted milk," therefore, as used here, refers to a palatable emulsified fluid made of butterfat, of skim milk dehydrated at a temperature of 150° F. or below, and of water.

2. *Comparison with Fresh Milk*

Analyses of the reconstituted milk supplied us by Dr. Charles E. North were made in the laboratories of two of the members of the Subcommittee. These bear out the evidence of other laboratories that the chemical and nutritional components of reconstituted milk are the same as of fresh milk except that there is a diminution of vitamin C. The pH of the milk as well as the mineral content, although varying slightly from sample to sample, appeared to correspond with those in fresh milk.

The methods of production of reconstituted milk are wholly susceptible to adjustments with regard to the amount of

butterfat in the milk and as to sanitary requirements. Reconstituted milk can be pasteurized in the same way as ordinary milk. The quality of the constituents of the milk can be adequately supervised. In other words, nutritionally, chemically, and bacteriologically, and by taste, reconstituted milk can be made the equal of natural milk. In saying this the Subcommittee is not concerned with the question of whether or not reconstituted milk should be encouraged where ordinary milk is available in adequate quantities to meet the needs of the community.

3. *The Field of Usefulness of Reconstituted Milk*

The greatest field of usefulness for reconstituted milk is in areas removed from dairy cattle regions, in sub-tropical and tropical climates, and on ships and in army cantonments under war conditions. It can be used as a subsidiary supply in large communities during periods of milk shortage, and, if it be true that it can be sold at much lower prices than regular fluid milk, its availability to people of small income may become a matter of considerable importance.

By dehydrating skim milk and storing it for future use during the spring and early summer when milk is particularly abundant and rich in butterfat, the national economy is improved and wastes are eliminated. It must also be borne in mind that reconstituted milk can be made anywhere by the use of proper apparatus and thus the need of shipping water in milk is obviated.

4. *Experiments with Reconstituted Milk*

During the latter part of World War I the subject of milk dehydration and of milk reconstitution aroused great interest. Experiments in the use of reconstituted milk were carried out, including clinical tests at the Babies' Hospital in New York and elsewhere. The experiments showed that adults as well as babies can thrive on reconstituted milk made of properly safeguarded ingredients.

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Original Articles

by

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THE EVOLUTION OF OUR PRESENT KNOWLEDGE OF HYPERSENSITIVENESS*

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I N the light of the fact that the hypersensitive reactions are often of startling intensity and the onset of symptoms most sudden, it is not to be wondered at that the noticeable contrast between the reaction of the idiosyncratic and other persons against one and the same agent has commanded attention from time immemorial. The condition of hypersensitiveness per se was recognized at a very early period.¹ Greek and Roman authors described the phenomenon by the term "idiosynkrisie" which is used today. Galen employed the term "idiopathy." The thought of the time, as is evidenced in this terminology, centered about attempts to gain an insight into constitutional deviations of the idiosyncratic, emphasis apparently being placed upon individual disposition rather than upon environmental factors. Though the dawn of the twentieth century ushers in the true beginnings of our present knowledge of allergy, we might pause a moment to reflect that no new discovery is ever so entirely original that it does not have its roots in the past.

Elliotson,² in London, in 1831, was the first to seek an etiologic factor in the pollens of the blossoming grasses. This work, taken up by Blackley³ in Manchester in 1873, was greatly extended by the latter's use of the "skin and mucous membrane tests," inoculation of flower dust into scarified skin, and inhalation of pollen. Blackley's publication stated that a disease described by John Bostock⁴ in 1819 as a "periodical affection of eyes and chest" and later as "catarrhus aestivus" was viewed etiologically as a "pollen catarrh" and that this was related to those idiosyncrasies which were known even in Galen's time as "rose cold." There was little opposition to the "pollen theory." Dunbar,⁵ in 1903, confirmed the findings of Elliotson and Blackley and corrected the impression of the English authors on two important points, namely, that hay fever sufferers were hypersensitive during the non-pollinating sea-

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son, and, secondly, that there was a relative specificity of pollen idiosyncrasy.

Some of the early observations are of interest in showing how inevitable the discovery of anaphylaxis was with the introduction of the experimental method. Scattered communications appeared which were concerned with increased reactions produced by repeated injections of foreign materials. In 1890, Koch⁶ first clearly demonstrated the phenomenon of hypersensitivity to a specific substance in his experiments with tuberculin. We glean from Morgenroth⁷ that in 1839 Magendie observed that white rabbits easily tolerated a first injection of albumin but that some days later they could not tolerate the injection of a similar dose. Flexner⁸ (1894), too, observed that rabbits, surviving a first injection of dog serum without a symptom, some days or weeks later died when given an equal or even smaller dose. Behring,⁹ in 1893, studying the effects of diphtheria toxin on guinea pigs, showed that these animals, once injected with the toxin, became in certain cases intensely sensitive to it; but he did not consider the phenomenon either general among the injected animals or common to all poisons. Studying immunity particularly, he considered hypersensitivity a "paradoxical reaction." He made the statement that horses, under immunization, possessing large amounts of antitoxin in their blood showed hypersensitivity to the toxin. These animals in all probability did not develop symptoms referable to the specific action of the toxin injected, for toxin is never injected in a pure state. The symptoms were, therefore, most probably due to the associated materials in the media. In 1894, Arloing and Courmont¹⁰ noted that successive injections of donkey serum produced toxic effects in man. Courmont,¹⁰ in 1900, noted that on inoculating guinea pigs with successive and very weak doses of the effusion of tuberculous pleurisy, the animals died before receiving a quarter of the total dose they originally took as a single injection, without ill effect.

These investigators did not realize that they had stumbled upon a phenomenon not heretofore described or named. It was Charles Richet,¹¹ the French physiologist, who in 1902 recognized the novelty of the phenomenon so many others had chanced upon yet did not comprehend, and it was he who correlated his observations and followed them out to their logical conclusions.

Yet, it is interesting to recall that in 1898 Richet¹² himself com-

pletely missed his opportunity while he and Héricourt were studying the effects of eel serum on dogs. He noticed that the second injection, and the third even more markedly, made them sick and waste away. Richet admitted later that he did not understand the significance of this result and contented himself with supposing there was increased sensitivity without attempting to analyze the phenomenon. Opportunity knocked at his door once again, which happens more often than we are ready to believe. As Richet¹³ so aptly remarked in his book, "The Natural History of a Savant," one can work a life time on a problem and develop nothing of fundamental importance, yet occasionally one may chance upon a great discovery after but a short period of work. So it was with his discovery of anaphylaxis. He chanced upon a phenomenon in biology which bids fair to take its place amongst the great discoveries and for which he received the Nobel Prize. It has opened the door to the understanding of a host of conditions which afflict mankind. In this sense then we can say that the dawn of the 20th century is the true beginning of our basic knowledge of hypersensitiveness.

Richet's¹⁴ discovery was made in the course of his study of toxins with which he attempted to immunize dogs. Animals which withstood the lethal dose were later again injected with the same toxin. It was these reinjection experiments which drew his attention to the peculiar phenomenon to which he gave the name "anaphylaxis." The experiment which led to his discovery will be briefly quoted here.

"During a cruise on Prince Albert of Monaco's yacht, the Prince and G. Richard suggested to P. Portier and myself a study of the toxic properties of the *Physalia* found in the South Seas. On board the Prince's yacht experiments were carried out, proving that an aqueous glycerin extract of the filaments of *Physalia* is extremely toxic to ducks and rabbits. On returning to France, I could not obtain any *Physalia* and decided to study comparatively the tentacles of actinaria, which resembles *physalia* in certain respects and are easily procurable. Owing to the kindness of Y. Delage, I was able to obtain a large quantity; the tentacles cut close to the body were placed in glycerin and thus we had in Paris several liters of an intensely toxic fluid, the glycerin dissolving and extracting the active principle. While endeavoring to determine its toxic dose, we soon discovered that some days must elapse before fixing it, for several dogs did not die until the fourth or fifth day or even later after administration. We kept those which had been given a dose insufficient to kill, in order to carry out a second investigation upon them when they had completely recovered.

"At this point, an unforeseen event occurred. The dogs which had recovered were intensely sensitive and died a few minutes after the administration of subsequent small doses.

"The most typical experiment, that in which the result was indisputable; was carried out on a particularly healthy dog named "Neptune." He

was given at first 0.1 c.c. of the glycerin extract without becoming ill; twenty-two days later, as he was in perfect health, I gave a second injection of the same amount. In a few seconds, he was extremely ill; breathing became difficult, and he was panting. He could scarcely drag himself along, lay on his side, was seized with diarrhea, vomited blood, sensibility diminished, and he died in twenty-five minutes."

It has always been a source of wonder to me that Richet should have discovered anaphylaxis with a substance that was highly toxic and that this discovery should have been consummated in the dog, for Weil¹⁵ and others have since shown that anaphylaxis is difficult to induce in the dog.

Richet's observation was first attributed to toxin accumulation, and yet, he stated that the symptoms of this reaction differed greatly from primary intoxication studies. His systematic investigations revealed that the described phenomenon is produced at least 2 or 3 weeks after the first injection, which definitely excluded the cumulative concept. Richet determined that the first toxin injection in his animals not only caused no antitoxic immunity but rather that it produced an increase in the toxin sensitivity which was manifested after the course of a certain incubation period. The first toxin injection did not act "prophylactically" in these animals, but in contrast, as Richet termed it, "anaphylactically." The first toxin injection transformed the animals into a state of "anaphylaxis" (without protection).

On the heels of Richet's discovery came Arthus¹⁶ (1903) who demonstrated that a non-toxic protein may also produce hypersensitiveness. According to the pioneer observations of Arthus, rabbits react neither to subcutaneous, intraperitoneal nor intravenous primary injections of horse serum. On the other hand, when rabbits previously sensitized to horse serum are reinjected intravenously, very severe symptoms appear almost immediately which may lead to anaphylactic death in two to four minutes. If the horse serum is injected subcutaneously at six-day intervals, resorption of the serum takes place after the first three of such injections. However, after the fourth injection, infiltration appears which finally develops into necrosis, sequestration and abscess formation. This, Arthus described as local anaphylaxis, known today as the "Arthus Phenomenon." The use of the terms "local" and "general" anaphylaxis leave no doubt that Arthus identified his observations with those of Richet.

His experiments were successful not only with horse serum but also

with cow's milk. However, rabbits sensitized with the one substance were unharmed by the other, thereby demonstrating the specificity of anaphylaxis. Since Richet and Arthus resorted to such varied stuffs as the toxic actino congestin and nontoxic cow's milk and horse serum, it became evident that anaphylaxis could be produced with substances which are very different from each other in chemical properties and in physiological action.

Many substances and various animal species were subsequently used to demonstrate anaphylaxis and yet, not until the guinea pig was utilized were really decisive results obtained. The guinea pig became the experimental animal of choice in this field after Theobald Smith¹⁷ made the following observations (1905). In the course of his work on the standardization of diphtheria antitoxin, Smith noted that guinea pigs, which several weeks before had received a dose of diphtheria toxin and antitoxic horse serum, showed severe symptoms or died immediately after reinjection with several cc. of normal horse serum. Ulrich Friedemann¹⁸ who was working in Ehrlich's laboratory informs me that although such reactions in guinea pigs to repeated injections had been observed for some time, no particular interest was evoked until Ehrlich returned to his laboratory in Germany after a visit to Smith in America. He suggested to Otto,¹⁹ one of his assistants, that he work on this problem. Otto called it the "Theobald Smith Phenomenon." One is tempted to feel that Otto, the German, preferred to credit an American rather than the Frenchmen, Richet and Arthus, with this fundamental discovery.

Because of the ease with which this phenomenon could be produced in the guinea pig, the work stimulated by Smith awakened a tremendous and widespread interest in the subject of hypersensitiveness. The same conclusions as Smith's were drawn by Rosenau and Anderson²⁰ in America, and in rapid succession by many others.

The first recorded foreign serum injection into man, that of lamb blood, was given in 1667, by Deins.²¹ No ill effects were ascribed to this introduction of foreign serum, until the beginning of the 19th century, when the intravenous introduction of lamb blood was discovered to be accompanied by grave danger, resulting in high fever, emboli, bleeding and hemoglobinuria. The cause for these reactions was first explained by Landois²² and Ponfick, in the latter part of the 19th century, but their explanations were concerned with incompatibility of blood cells. At about this time, urticarial eruptions were observed to occur several

days after transfusions. Dallera²³ described a case of a girl with "hysterical mania" whose whole body was covered with urticaria ten days after transfusion. Other reports soon followed. Because of the ill effects of lamb blood transfusions, animal blood transfusions were almost completely abandoned. Dominicis,²⁴ in 1895, tried to revive their use. Milk transfusions were also attempted but soon disappeared from medical annals because they were found to be useless and dangerous.

Since Pasteur's discovery, in the middle of the 19th century, that infectious agents are the cause of certain diseases, attempts have been made to aid the body in specifically neutralizing invading bacteria and accelerating the mechanism of immunity. This has given rise to the use of antitoxic and antibacterial sera obtained from other animal species. In 1894, the treatment of diphtheria with antitoxic horse serum had been introduced by Behring.

Lublinski²⁵ was probably the first to publish a case of exanthem after the injection of a therapeutic serum. An eight-year old girl, on the second and third days of her illness, received injections of 0.3 cc. Behring's diphtheria antitoxin. On the fifth day of her illness there was a red area around the site of the injection. Nine days after the last injection she developed high fever, multiple and painful joint swellings with a widespread multiform erythema and a macular eruption. This severe syndrome lasted for four days. With the recession of the exanthem the joint pains and swelling diminished.

Experimentally Johannessen²⁶ gave proof that the active agent in the production of these sequelae was not inherent in the antitoxic content, but something in the horse serum itself since the same symptoms were produced in non-diphtheritic persons with normal horse serum. A large number of publications appeared in the literature with respect to this syndrome which was called "serum exanthem" because of the cardinal symptom of skin eruption.

But no careful analysis of this condition was made until von Pirquet and Schick²⁷ published their classic monograph in 1905, "Serum Krankheit." The new term, serum sickness, included all the other symptoms besides the exanthem. They explained the clinical manifestations in the following way. Foreign serum acts on man as an antigen. Antibody, which develops in the organism as a result of the antigen, upon union with the horse serum produces the symptoms. Serum sickness is therefore an in-vivo, antigen-antibody reaction. The incubation period de-

pend upon the completion of the appearance of the antibodies and the presence of horse serum still remaining in the blood.

An important step in linking up the mechanism of serum sickness with allergy was the work of Hamburger and Moro²⁸ who, in 1903, demonstrated that precipitins resulted after the introduction of foreign serum.

Little notice might have been taken of the experiments of Richet and Arthus on anaphylaxis in its application to man had not von Pirquet and Schick found that *reinjection* of serum at some later date results in immediate and accelerated reactions, which phenomenon they called "allergy"—altered reaction. Charles Richet did not easily forgive von Pirquet for coining the term allergy, for, he argued, is not anaphylaxis sufficient to describe the phenomenon in both animal and man? One can appreciate his feelings, but usage and euphony have given to allergy the greater popularity. Furthermore, von Pirquet²⁹ used the term allergy in a broader sense than Richet, who considered anaphylaxis only from the standpoint of hypersensitiveness to foreign proteins. von Pirquet included all reactions to foreign proteins and infectious agents and laid the groundwork for our understanding of the relationship between allergy and immunity. One is in the best of company, however, whether one adheres to the term allergy, or prefers anaphylaxis.

The immediate character of the anaphylactic reaction described by Richet and Arthus would therefore in the light of von Pirquet and Schick's work be explained on the basis of the presence of previously formed antibodies. This conception of serum sickness and anaphylaxis as vital antigen-antibody reactions has served to elucidate many varied phenomena which at first appeared widely divergent but were later shown to depend on this basic concept. In the short period between 1902 and 1910 practically all the principles of hypersensitiveness were laid down.

One cannot deny that many diseases have been controlled through the use of antisera, but in their wake have come not only the relatively harmless serum disease, but the more serious serum allergy and anaphylaxis. Though the reaction to the invasion of foreign materials is purely a physiological one, the tempo of reaction is invariably accelerated. A knowledge of these reactions should lead to a more intelligent management of disturbed conditions that result paradoxically from a beneficent curative procedure.

For practical clinical purposes—so far as danger to life is concerned—

primary contact with foreign substances should always be carefully distinguished from secondary or repeated contacts. But, whether primary serum sickness or serum allergy are under consideration the basic similarity of their mechanisms must be kept in mind. Thus after primary contact with a foreign substance nothing transpires until an incubation period elapses, during which time specific antibodies are formed. When this supervenes, the foreign substance still present in the body reacts with the newly formed antibodies and the signs and symptoms of serum sickness become manifest in the different tissues. On the other hand, by allergy is meant the reaction which ensues when antibodies are present in the tissues as a result of previous contacts and when the specific antigen again enters the body a reaction takes place immediately or shortly thereafter without a prolonged incubation period.

Whether the invading foreign substance is a serum, food, inhalant, drug, or hormonal extract, the body response in each instance is fundamentally the same, differing only with respect to the tissues directly involved. From all of this, it must be apparent that the organism is so constructed that it continually impedes the invasion into the circulation of materials that cannot be utilized by the body economy. There are periods, however, when the organism fails to prevent the entrance into the body of inimical agents, such as bacteria, viruses, chemicals, toxins, and foreign proteins. When such invasions of foreign agents do occur, the organism may become either (1) damaged or destroyed, (2) allergic, or (3) immune.

There is a growing impression that allergy inevitably precedes a state of immunity.³⁰ Immunity, however, is not static, and an individual immune at one time may again become allergic. These changing conditions in the same individual depend largely on whether the antibodies are anchored to cells alone—the allergic state, or whether the antibodies are present in greater abundance in the circulation, neutralizing the antigen before it reaches the antibody containing cells—the immune state.

Another factor of great importance is that when the invasive substance is a viable antigen, such as a bacterium, it multiplies in the body and thus complicates the situation by destroying tissues through the production of endotoxins and exotoxins. On the other hand when the substance is not viable—serums, foods, pollens, etc.—and therefore non-multipliable, no destructive lesions result, and the reaction is dependent entirely on the actual amount of antigen which invades the body at that particular time.

The evolution of our present concept of allergy is thus unfolded. But a small part of the story has been told, as may well be imagined. Some may question my omission of such developments as the anaphylotoxin theory, the protein cleavage concept, atopy, the histamine basis for allergy, the Schultz-Dale phenomenon, Otto's and others' work on passive anaphylaxis, the heterophile studies by Friedemann and others, the work emanating from the Prausnitz-Küstner phenomenon, and our own work on congenital hypersensitiveness and experimental asthma. My main purpose, however, was to show that this subject—whether we speak of it as hypersensitiveness, allergy, anaphylaxis, atopy or any other term that has been devised—is not young. The course of its growth has not been direct, and amongst the deviations have been the developments above named. Each has undoubtedly added something to our general knowledge, but to them we must assign a minor role.

As I see it, the major role in this ubiquitous drama is played by the antigen-antibody tissue reaction. We may sum it up simply as follows. A substance, foreign to the body economy, which in and of itself is harmless when entering the body for the first time, may produce a disturbance upon subsequent invasion. This is due to an interaction between the specific antigen and its related antibody which has been elaborated and become fixed to the smooth muscle cells of some organ or organs in the interim between the primary and secondary invasions of the antigen. The union produces cellular irritation with concomitant spasm and probable physico-chemical reactions of the sensitized tissue.

The type of syndrome produced depends upon the characteristics of the tissue irritated. Such a unitarian concept is supported by a wealth of sound observation. It enables us to conceive how such varied syndromes as serum sickness, eczema, hay fever, asthma, disturbances of the gastrointestinal tract, central nervous system, the liver and other organs, are all manifestations of the one phenomenon—a simple union of antigen and antibody with differing chemical, physiological and pathological secondary effects.

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BULLETIN OF
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SEPTEMBER, 1942

PHYSIOLOGIC STUDIES PERTAINING
TO DEEP SEA DIVING AND AVIATION,
ESPECIALLY IN RELATION
TO THE FAT CONTENT AND
COMPOSITION OF THE BODY

The Harvey Lecture, March 19, 1942

LIEUTENANT COMMANDER ALBERT R. BEHNKE, JR.
(MC), U. S. NAVY

THE environment again concerns the investigator. Beginning with the studies of Paul Bert, Heller, Mager, von Schrötter, and Haldane knowledge has accumulated slowly upon the effect of high pressures on the diver and caisson worker. The investigations conducted in the physiology laboratory of the Harvard School of Public Health in collaboration with the late Louis A. Shaw, and then at the Experimental Diving Unit, Navy Yard, Washington, D. C., have served to make possible rescue and salvage operations incident to a submarine disaster.

Recently these studies have clarified some of the puzzling phenomena observed in high altitude flight. In this lecture I shall outline the physiologic factors that enable divers and aviators to work in a pressure environment of 16 atmospheres or in a rarefied medium of 0.20 of an atmosphere, respectively. Of especial interest are the quantitative studies

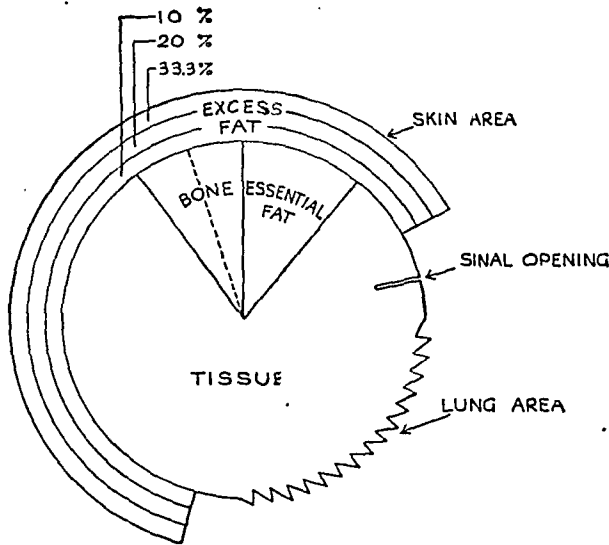


Fig. 1—Schematic representation of the body showing the volumetric relationship between the excess fat and the true body mass.

These data form the basis for the diagram—

Analysis of the true body mass, specific gravity=1.099

| <i>Substance</i> | <i>Specific Gravity</i> | <i>Weight % Total mass</i> | <i>Volume % Total mass</i> |
|---------------------|-------------------------|----------------------------|----------------------------|
| Bone | 1.560 | 15 | 10.5 |
| Essential Fat | 0.940 | 10 | 11.7 |
| Tissue | 1.060 | 75 | 77.8 |

The addition of excess fat amounting to 10 per cent of total body weight reduces the specific gravity of the true body mass from 1.099 to 1.080; 20 per cent additional fat lowers the specific gravity to 1.062; and 33.3 per cent additional fat lowers the specific gravity to 1.036.

pertaining to the absorption or elimination of gaseous nitrogen which in turn have permitted estimates of fat content and composition of the body of the healthy, adult male.

With reference to the schematic diagram, Figure 1, protoplasm can be compressed or placed in a rarefied atmosphere without demonstrable effect provided that the pressure is equally distributed. Since air or other gaseous media are necessary for compression, interference with the free movement of gas, particularly in the channels leading to sinal and aural spaces, dilates blood vessels and produces hemorrhage into the occluded spaces. These painful but circumscribed effects of pressure are of minor importance, however, compared with the physiologic response brought about by the disturbance in gaseous equilibria whenever pressure fluctuates.

I. THE MAJOR EFFECTS OF HIGH BAROMETRIC PRESSURE

1. *Nitrogen Narcosis*.—As the pressure is raised in an air atmosphere the ambient gases are absorbed by the circulating blood and transported to the other tissues of the body. Apart from the possible difficulty in opening the normally closed auditory tubes, it is perceived that as the air is warmed by the heat of compression, its increased weight calls forth greater respiratory effort which may interfere temporarily with the normal elimination of carbon dioxide. The outstanding phenomenon is that the previously normal individual loses his ability to function efficiently.^{1,2}

Thus, the individual subjected to a pressure of 4 atmospheres, equivalent to a diving depth of 100 feet, begins to experience symptoms not unlike those elicited by altitude anoxia or alcoholic intoxication. Experienced divers, for example, are able to estimate diving depth within a range of 25 feet "by the way they feel." This feeling manifests itself as an impairment in neuromuscular coördination as well as a slowness and unreliability in cerebration. Essentially greater effort is required to perform work.

The agent responsible for the narcosis is "atmospheric nitrogen" including argon. When pure oxygen instead of air was breathed at a depth of 100 feet, the retardation, at least for short periods of time and prior to the onset of the symptoms of oxygen poisoning, was minimized. The employment of helium, moreover, to replace atmospheric nitrogen abolished or rendered negligible the adverse effect and proved that a rather ideal atmosphere could be created compatible with efficient work at depths up to 500 feet, and at a pressure not supporting consciousness were air breathed. By contrast, when argon was substituted for atmospheric nitrogen, the inhaled mixture at high pressures elicited reactions similar in type but more intense than those manifest in compressed air. Elementary gases, therefore, that are wholly innocuous at normal pressures may render an individual completely helpless in a high pressure atmosphere.

The explanation of the action of nitrogen and argon is to be sought in some physical property since argon does not possess valence and hence like helium, is incapable of entering into any stable chemical combination. Of the obvious physical properties solubility in oil and molecular weight may be important.

TABLE I

ARGON, HELIUM, NITROGEN, AND OXYGEN SOLUBILITY IN WATER
AND IN OLIVE OIL AT 38° C., AND THE RESPECTIVE
OIL WATER SOLUBILITY RATIOS

| <i>Water</i> | | | |
|------------------------------------|----------|----------|---------|
| Argon | Helium | Nitrogen | Oxygen* |
| 0.0262 | 0.0087 | 0.0127 | 0.023 |
| <i>Olive Oil</i> | | | |
| Argon | Helium | Nitrogen | Oxygen |
| 0.1395 | 0.0148 | 0.0667 | 0.112 |
| <i>Oil Water Solubility Ratios</i> | | | |
| Argon | Nitrogen | Helium | Oxygen |
| 5.32: 1 | 5.24: 1 | 1.7: 1 | 4.9: 1 |

* Sendroy, J., Jr., Dillon, R. T. and Van Slyke, D. D. *J. Biol. Chem.*, 1934, 105:597.

The data in Table I are in accord with the Meyer-Overton hypothesis relating anesthetic effectiveness to fat solubility. The consideration that the higher molecular weights of nitrogen and argon might interfere with cellular gaseous metabolism particularly with carbon dioxide diffusion and transport has not yet been supported by experimental data.

The employment of hydrogen with a solubility coefficient in oil considerably higher than that of helium, may lead to the solution of the problem, or at least to an evaluation of the role that fat solubility in comparison with molecular weight assumes in the etiology of this type of narcosis.³

2. *Phenomena of Oxygen Poisoning.*—The increased partial pressure of oxygen in the air at great depths, the employment of oxygen as the basis for the decompression of divers and the treatment of compressed air illness, have necessitated extensive tests of oxygen tolerance.

At a pressure of 1 atmosphere pure oxygen has been inhaled by healthy men for periods as long as 17 hours without injurious effects. On the other hand, some individuals have complained of substernal distress and irritability following the inhalation of pure oxygen for periods of 7 hours. In one individual sensitivity to oxygen was manifest by the formation of wheals, dermatographia, flushing of the face, and later by

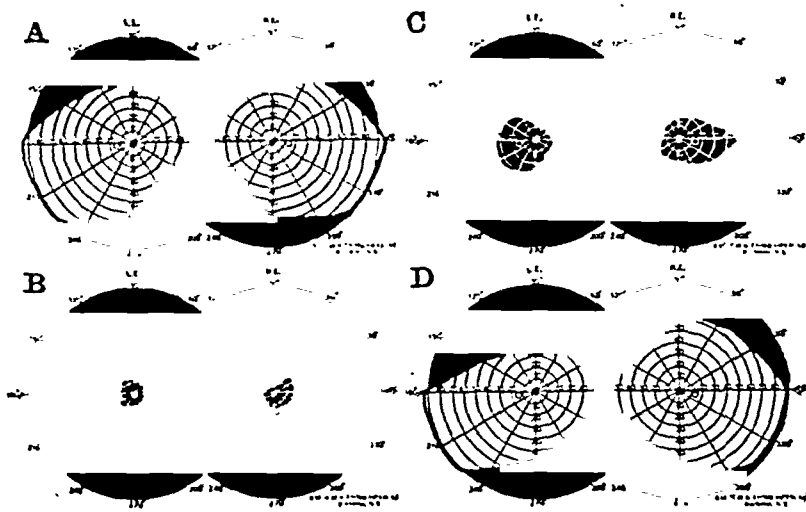


Fig. 2—Perimetric measurements made before and after $3\frac{1}{2}$ hours' oxygen breathing at 3 atmospheres' pressure (30-lb. gauge). A, normal field limits; determinations made with the Ferree-Rand perimeter and exposure method with 7 foot-candles illumination. B, C, and D, field limits 5, 25, and 50 minutes, respectively, following $3\frac{1}{2}$ hours' oxygen breathing; observations made at atmospheric pressure with a black perimeter of 25 cm. radius illuminated by a blue bulb placed behind and above the observer's head; moving stick stimuli were used and checked by the exposure method; test object was a white disc 6 mm. in diameter. From Behnke, Forbes, and Motley, *Am. J. Physiol.*, 1935-36, 117:436.

the development of dermatitis. Remission of symptoms was hastened by the administration of histaminase. The action of a histamine-like substance, as postulated by Campbell,⁴ explains many of the toxic symptoms associated with the inhalation of oxygen and suggests an approach to the solution of the problem.

At a pressure of 3 atmospheres the oxygen taken up by the blood in physical solution is sufficient to meet tissue requirements so that hemoglobin is not reduced.⁵ Periodic waves of nausea constitute the most frequent symptom at this pressure together with the appearance of facial pallor. Progressive contraction of the visual fields terminating in a transient amblyopia has been repeatedly observed during the fourth hour of exposure.⁶ Although vision is temporarily lost, a measure of consciousness is retained and recovery begins immediately upon the substitution of air for oxygen as illustrated by Figure 2.

Whenever doubt arises as to the habitability of a given environment, the decisive criterion is ability to work. An excellent test therefore of

resistance to the toxic effects of oxygen at a pressure of 3 atmospheres consists in having subjects exercise on a bicycle at a rate sufficient to increase oxygen consumption fourfold over the basal state. Test runs of this character are usually terminated after 15 to 20 minutes by extreme fatigue, numbness of the lower extremities, and in one instance by an abortive convulsive seizure. In control runs this type of exercise can be maintained without undue fatigue for a period of one hour.

In man, at a pressure of 4 atmospheres severe convulsive seizures occur after about 45 minutes of oxygen inhalation. Perhaps no other induced physiologic disturbance of comparable severity is followed by such prompt and complete functional recovery. Essentially oxygen induces transient idiopathic epilepsy in the apparently normal individual.

For periods of 27 minutes men have repeatedly inhaled oxygen at 4 atmospheres pressure with no other symptoms than a sensation of cerebral fulness and some degree of mental torpidity. Under these circumstances the excess quantity of oxygen taken up by the blood stream and held in solution in the tissues during a period of 17 minutes may augment oxygen absorption by 159 cc. per minute, a 55 per cent increase compared with the consumption during a control period. In the circulating blood of dogs exposed to 4 atmospheres pressure the oxygen in physical solution in arterial blood was 7 volumes per cent while the oxygen dissolved in the mixed venous blood was at times as high as 3.6 volumes per cent.

In the dog repeated daily seizures over a period of 21 days do not exert a detrimental effect on the well-being of the animal in that weight remains constant, appetite and muscular activity are unchanged. The tests indicate that tolerance for high oxygen pressure is developed because the exposure time necessary to produce the seizure is increased. Of particular interest are the recurrent strychnine-like seizures indicative of involvement of the spinal cord. During these attacks which are particularly apt to occur during the second diurnal exposure, the eyes turn outward, the whole body becomes rigid, the extremities spread apart, and opisthotonus supervenes. Tetanic contractions of the diaphragm stop respiration. These attacks may recur from four to twelve times per minute. The reflex excitability of the nervous system is greatly heightened since tactile, auditory, and visual stimuli serve to initiate the tetanic seizures.

Although these disturbances are severe, in view of the rapid recovery and the considerable latent period preceding onset of the symptoms, it has been possible to utilize oxygen in the prevention and treatment of compressed air illness.

3. *Field Application.*—The observations made in the laboratory soon governed field practice during diving operations in submarine disasters.

In 1939, divers breathing air at a depth of 240 feet in salvage work on the U.S.S. *Squalus*, suffered lapses of memory, mental confusion, and occasionally loss of consciousness. It proved to be not only dangerous but futile to work within a maze of hose and cables at a depth of 240 feet in an atmosphere of air.⁷

As in the laboratory, so also in the field, the substitution of helium for nitrogen rendered negligible the impairment in neuromuscular co-ordination and enabled divers to work efficiently when under 7 atmospheres of pressure. The successful termination of the salvage operations was made possible only by the employment of helium.

In 1940 a second submarine disaster occurred in water 440 feet deep. Although the pressure at this depth was sufficient to crush the hull of the disabled craft, divers breathing a mixture of helium and oxygen reached the bottom and were able to survey the sunken vessel. These divers, in spite of subjection to a pressure of 14 atmospheres, felt well and had little difficulty in performing the work required in descent and ascent to a depth corresponding closely to the height of the Washington monument.

II. MANNER OF ABSORPTION OR ELIMINATION OF INERT GAS

1. *Animal Experiments.*—The basic consideration concerned with existence in an abnormal pressure environment is the absorption and subsequent removal of inert gas. In this connection all of the gaseous nitrogen appears to be dissolved in fluids and fat in the ratio of 1 to 5 except for a small additional amount due to the presence of hemoglobin in solution. This molecular nitrogen can be removed from the tissues and measured if the body is placed in an oxygen atmosphere. Knowing the volume of the system and taking periodic samples it is not difficult to ascertain the quantity of nitrogen originally present in the tissues.

Dogs anesthetized by the injection of a suitable drug serve well for such experiments. If the first 7 minutes of an experiment be utilized to

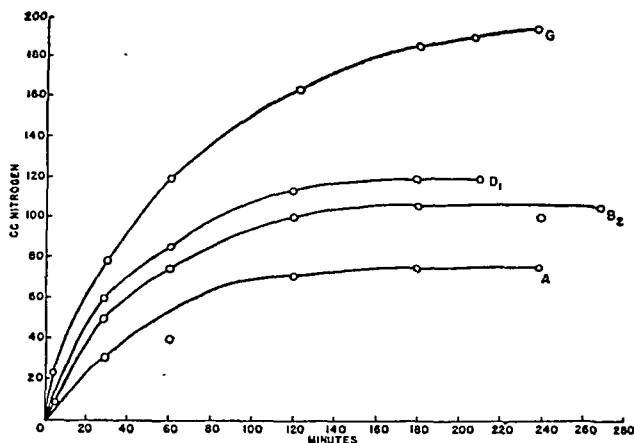


Fig. 3—Nitrogen elimination from 4 dogs placed in an oxygen atmosphere at normal pressure. During the first 7 minutes of oxygen inhalation the lungs and apparatus were rinsed free from nitrogen. (From Shaw, Behnke, Messer, Thomson, and Motley, *Am. J. Physiol.*, 1935, 112:545.)

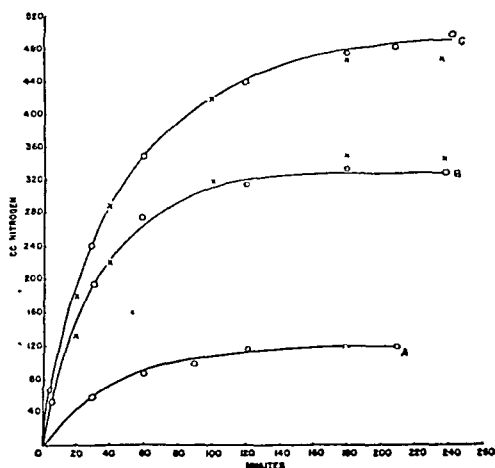


Fig. 4—The nitrogen elimination of dog "D" following equilibrium exposures in air at 1, 3, and 4 atmospheres of pressure. The nitrogen eliminated during the first 8 minutes of oxygen inhalation was not collected. Curve A, desaturation from 1 atmosphere; curve B, desaturation from 3 atmospheres; curve C, desaturation from 4 atmospheres. O, experimental values; X, theoretical values. (From Shaw, Behnke, Messer, Thomson, and Motley, *Am. J. Physiol.*, 1935, 112:545.)

rinse the lungs and apparatus free from nitrogen, then during a subsequent period of 3 to 4 hours the dog's body becomes nitrogen free.⁸ Figure 3 represents a number of nitrogen elimination curves obtained on several dogs subjected to such a procedure at normal barometric

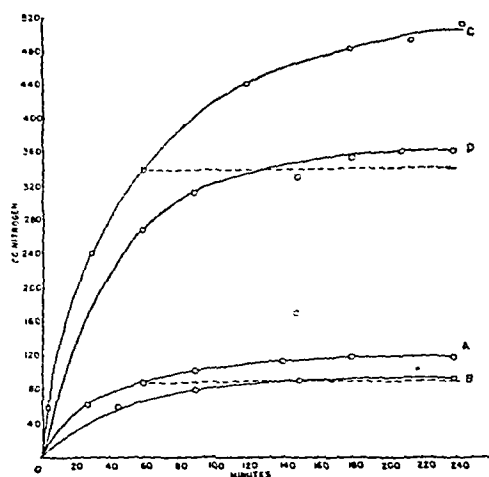


Fig. 5—Saturation time compared with desaturation time. Dog "D." The nitrogen eliminated during the first 7 minutes of oxygen inhalation was not collected. Curve A, follows complete saturation at 1 atmosphere; curve B, follows 67 minutes' saturation at 1 atmosphere; curve C, follows complete saturation at 4 atmospheres; curve D, follows 67 minutes' saturation at 4 atmospheres. (From Shaw, Behnke, Messer, Thomson, and Motley, *Am. J. Physiol.*, 1935, 112:545.)

pressure. The fact that dog "G" was fat and dog "A" was lean is reflected by the large difference in the nitrogen content of the dogs in proportion to body weight.

If the dog is now placed in compressed air until saturation with ambient nitrogen has been attained, the nitrogen absorbed can be collected in the manner previously described. From a series of exposures in compressed air, utilizing the same dog "D," it was observed from the plotted data of Figure 4 that the amounts of nitrogen recovered following decompression from 3 and 4 atmospheres respectively, were proportional to the pressure. These results are in accord with Henry's law.

In another series of tests the rate of nitrogen absorption was compared with that of nitrogen elimination. Dog "D" was first rendered completely nitrogen free in the manner represented by curve A, Figure 5. For a period of 60 minutes the dog breathed air and following the air inhalation it was again placed in an atmosphere of oxygen. The amount of nitrogen absorbed during the 60-minute period of air inhalation, curve B, Figure 5, is equal to the quantity originally eliminated during the same period of time.

The same type of experiment was repeated at a pressure of 4 atmos-

pheres and again it was demonstrated that within the limits of experimental error, the manner of nitrogen transport is the same either to or from tissues.

Gaseous Nitrogen in Relation to Fluid and Fat Content of the Body.—If the body of dog "D" be subjected to analysis for the quantity of water, fat, and solid constituents, these values are obtained, body weight = 12.234 K., weight of fat* = 1.889 K., weight of dry solids = 3.117 K., weight of water (by difference) = 7.228 K. If these weights are multiplied by the appropriate solubility coefficients, the total nitrogen content of the body can be computed. Corrected for a pressure of 570 mm., for the density of fat, and for the decreased solubility of gas in body fluids when other dissolved substances such as salts are present, the coefficients adapted from Table I, are 52 cc.** per kilo of fat and 9 cc.† per kilo of fluid.

The nitrogen dissolved in the fat therefore is equal to 1.89×52 , or 98 cc., and in fluids, 7.23×9 , or 65 cc. The total nitrogen is 163 cc. or 1.3 cc. per kilo of body weight.

The quantity of nitrogen recovered from dog "D" was 124 cc. The difference between 163 and 124 cc. represents the estimated quantity of nitrogen given up during the first 7 minutes or rinsing period, and is in agreement with values based upon extrapolation of the experimental curve, that is 30 ± 5 per cent of the body total.

In practice, in order to avoid the use of extrapolated values, the quantity of nitrogen for the 7-minute period is taken as equal to the measured quantity obtained from the seventh to the twentieth minute as shown in columns 5 and 6, Table II.

The total nitrogen content of the body as measured by our technique, is distributed between fluid and lipid constituents of tissues.

Estimation of the Fat Content of the Body on the Basis of Measurements of Nitrogen Elimination.—In laboratory studies of gas absorption or elimination, it is of great importance to obtain an accurate estimate of the fat content of the body. From the discussion in the previous paragraph it is apparent this estimate can be made on the basis of meas-

* Substances soluble in carbon tetrachloride.

** In the original paper a value of 55.7 cc. was used on the basis of analysis of omental dog fat. In all subsequent analyses we have used olive oil as a more convenient solvent since it has an absorbing capacity similar to that of body fat for nitrogen.

† In the original paper the value of 9.54 was used as the nitrogen solubility coefficient in water. It is more appropriate for body fluids, however, to use a coefficient approaching the solubility of nitrogen in serum. In urine analyses there is a decrease of 0.01 volume per cent of nitrogen for every two units increase in specific gravity. The value of 9 is closer to the true value than 9.54.

TABLE II

ESTIMATION OF THE FAT CONTENT OF THE DOG'S BODY ON THE BASIS
OF THE MEASUREMENTS OF THE NITROGEN DISSOLVED IN THE TISSUES

| Dog | Weight (1) | Weight of fluids (60% body wt.) (2) | Nitrogen capacity of fluids (3) | Nitrogen capacity of fat (4) | Total nitrogen capacity of body | | | Weight of fat (8) | Weight of excess fat (9) | True body weight (10) | Fluid percent- age of true body weight (11) |
|---------------|---------------|---|--|---------------------------------------|------------------------------------|---------------|--------------|-------------------------|-----------------------------------|--------------------------------|--|
| | | | | | 0-7' (5) | 7'-20' (6) | Total (7) | | | | |
| | <i>kilos</i> | <i>kilos</i> | <i>cc.</i> | <i>cc.</i> | | | | <i>kilos</i> | <i>kilos</i> | <i>kilos</i> | |
| "D" lean | 12.23 | 7.23 | 65 | 98 | 39 | 39 | 163 | 1.89 | 0.70 | 11.5 | 62 |
| "A" very lean | 8.8 | 5.28 | 48(+3)* | 50(-3) | 24 | 24 | 98 | 0.96 | 0.09 | 8.71 | 61 |
| "B-2" lean | 11.3 | 6.78 | 61 | 81 | 38 | 38 | 142 | 1.56 | 0.48 | 10.8 | 63 |
| "D-1" lean | 11.9 | 7.14 | 64 | 104 | 50 | 50 | 168 | 2.00 | 0.90 | 11.0 | 64 |
| "G" fat | 13.8 | 8.28 | 75(-5)* | 183(+5) | 65 | 65 | 258 | 3.52 | 2.38 | 11.4 | 71 |

* Optional correction to make fluid percentage of the true body weight a constant value of 63.

urement of nitrogen recovered from tissues and a knowledge of the water content of the body. The variability, however, in the amount of fat in different individuals renders invalid the employment of fixed percentages to denote the relative amounts of such body constituents as water.

This difficulty can be overcome by dividing the fat into an essential portion comprising such substances as myelin in the spinal cord, fat in bone marrow, lecithin, cholesterol and other lipid or lipoid matter essential in body economy, and a portion consisting of excess adipose tissue.

If one considers then that there is a basic body structure exclusive of excess fat as constant in composition as blood, which constitutes the true body weight, this weight can be divided into the following relatively fixed percentages: for the dog, water=63, solid substances=27, and essential lipids=10; for man, reflecting in part the difference in integument, water=66, solid substance=24, and essential lipids=10.

For the percentage of water in the body a tentative value of 60 may be used based on the analysis of dog "D."

The true body weights then of a series of dogs as well as the amounts of excess fat can be computed in the following manner using the data from dog "D" as an example:

Body weight— $12.23 \times 60 = 7.23$ weight of fluids.

$7.23 \times 9 = 65$ cc. nitrogen in the fluids.

$163 - 65 = 98$ cc. nitrogen dissolved in fat.

$98 \div 52 = 1.89$ kilos, weight of body fat.

$10/9 (12.23 - 1.89) = 11.5$, true body weight.

$189 - 0.10 (11.5) = 0.70$, excess fat.

$7.23 \div 11.5 \times 100 = 63$, percentage of water in true body weight.

The analytical data for the series of dogs are presented in Table II.

An initial value for water content of 60 per cent of the gross body weight may require some correction if the percentage of fluids in relation to true body weight is to be maintained at 63. With reference to dog "G," for example, a value of 60 per cent of total body weight for water content results in a final percentage of water of 71 in the true body weight, column 11 (Table II). Having determined the gross amount of body fat, it is not difficult to make the minor corrections in the division of nitrogen so that the water percentage in relation

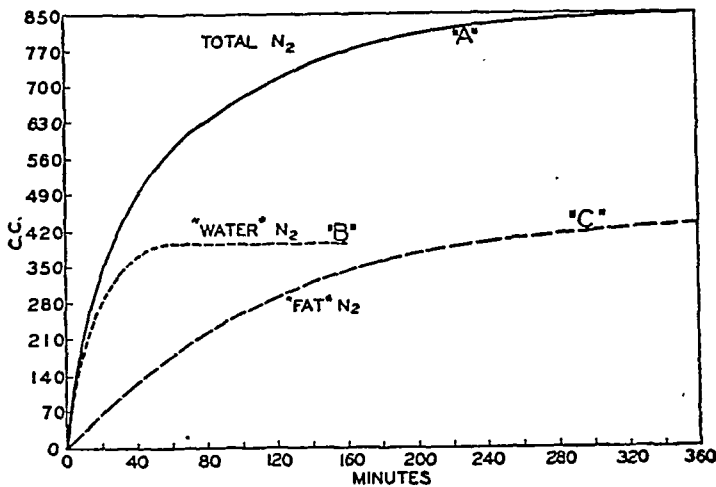


Fig. 6—Total N₂, A, represents the average of the values for nitrogen elimination from 3 men (average weight 64 k) who breathed pure oxygen at atmospheric pressure. "Water" N₂ (B) and "Fat" N₂ (C) are hypothetical curves showing the absorption or elimination of nitrogen by the body solvents. The values for nitrogen on A are approximately the sum of corresponding values on B and C. (From Behnke, *U. S. Nav. M. Bull.*, 1937, 35:219.)

to true body weight is 63. The large difference between the solubility coefficients of nitrogen in water and in fat permit this correction without invalidating the estimate for fat. Of primary interest is the method of analysis rather than the attempt to maintain any given, fixed percentages in the calculations.

2. *Measurements in Man.*—If a human subject is placed in an enlarged oxygen recirculating system similar to that devised for the dog,¹⁰ the gaseous nitrogen can also be removed from the tissues. Figure 6 shows the manner in which nitrogen is eliminated by lean men of comparatively small stature, average weight 64.2 kilos, if 99 per cent oxygen is inhaled for a period of 6 hours. It is observed that the rate of nitrogen output is about one-half of the corresponding rate for the dog, an anticipated finding in view of the comparative circulatory rates in relation to body weight.

If blood flow throughout the body were distributed uniformly with respect to the nitrogen content of tissues, the values of curve A could be derived from an exponential equation of the form $Y = (1 - e^{-kt})$ which expresses the relationship that a constant percentage of the nitro-

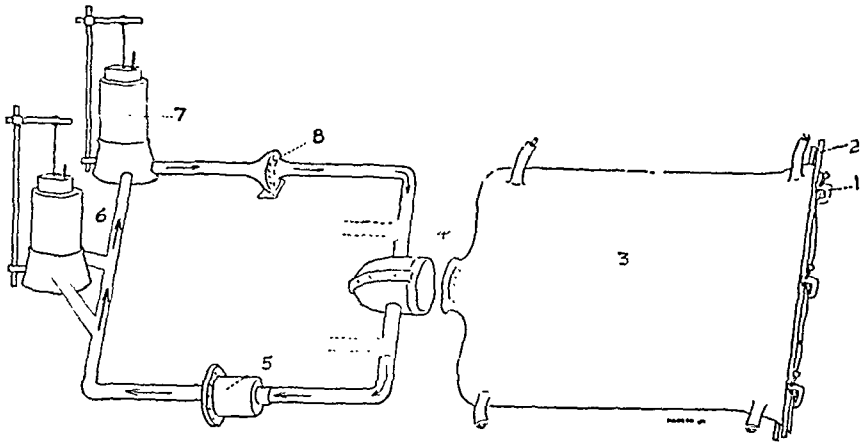


Fig. 7—Diagram of apparatus used to measure gas eliminated from the lungs and gas diffusing through the skin.

1, clamp on iron bars; 2, used to seal open end of rubber bag; 3, designed to fit around the body serving as a gas-tight seal; 4, rubber helmet and collar secured with adhesive tape around the subject's neck; 5, canister with absorbent for water and CO_2 cooled with ice; 6, spirometer for measuring added oxygen; 7, spirometer; 8, fan to circulate oxygen, bearing encased in oil to exclude air. Dotted lines indicate connections to a second similar system. (From Behnke and Willmon, *Am. J. Physiol.*, 1940-41, 131:627.)

gen present in the body is being eliminated throughout the entire period of oxygen inhalation. In the equation $Y =$ the amount of nitrogen eliminated during the time interval t ; $A =$ the initial nitrogen content of the body; $k =$ the rate of change in the slope of the curve; and e is the base of the natural logarithms. The expression, $1 - e^{-kt}$, gives the percentage decrease of nitrogen in the body during the time interval, t .

If the experimental values plotted on curve A, Figure 6, be substituted in the equation, the value for k is found to decrease progressively; a decrease that indicates that blood flow is not distributed uniformly in relation to the nitrogen content of tissues particularly in relation to fat which has a high nitrogen capacity and a poor blood supply. Thus, at the start of oxygen inhalation the average nitrogen pressure in the blood tends to fall below the nitrogen pressure in the fatty tissues which desaturate slowly. Consequently, the percentage rate of nitrogen elimination decreases.

However, if the total nitrogen content of the body is divided according to its solubility in water and in fat, then an equation can be applied similar to the one discussed in the previous paragraph but con-

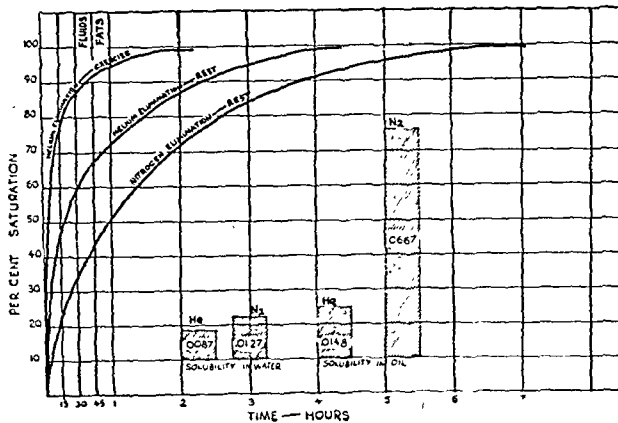


Fig. 8—Desaturation rate for man, comparing nitrogen with helium. During the first 45 minutes, gaseous removal takes place from the body fluids, and subsequently from the body fat. The solubility coefficients for helium and nitrogen are expressed as cubic centimeters of gas, reduced to standard conditions, dissolved per cubic centimeter of solvent, temperature 38° C.

sisting of two component parts, one for fat and the other for the body fluids. . . .

“Fluids”

“Fat”

$$Y = 364 (1 - e^{-0.098 t}) \text{ plus } 500 (1 - e^{-0.0085 t})$$

The values for k will vary for different individuals on the basis of elimination rate and division of nitrogen between water and fat.

The previously described tests were terminated at the end of 6 hours so that the endpoint for nitrogen elimination was not known with certainty. Several years later, by means of the system outlined in Figure 7, it was possible to collect nitrogen from the tissues for periods as long as 17 hours. Table III gives the results of a test in which the subject, a diver weighing 70 kilos, breathed oxygen for a period of 15 hours. The data plotted in Figure 8 agree well with those obtained in the earlier tests if allowance is made for the difference in fat content of the subjects.

2. *Cutaneous Diffusion of Gases.*—Diffusion as a fundamental property of gases would lead one to expect some movement of gaseous molecules through skin.¹¹ This can be demonstrated by the arrangement, Figure 7, to permit the inhalation of oxygen in a hood while the body is surrounded by the same or an indifferent gas. In a representative ex-

TABLE III

NITROGEN ELIMINATION FOR A DEEP SEA DIVER,
AGE 32, WEIGHT 154 POUNDS, HEIGHT 69 INCHES

| <i>Time</i> | <i>Total eliminated</i> | <i>Nitrogen† diffusion into system</i> | <i>Net nitrogen</i> |
|---------------------------|-----------------------------|--|---------------------|
| <i>min.</i> | <i>cc.</i> | | |
| 0-5* | (150) | | (150) |
| 5-65 | 481 | 47 | 434 |
| 65-70‡ | (25) | | (25) |
| 70-130 | 228 | 47 | 181 |
| 130-135‡ | (12) | | (12) |
| 135-195 | 158 | 47 | 111 |
| 195-200‡ | (7) | | (7) |
| 200-260 | 122 | 47 | 75 |
| 260-265‡ | (5) | | (5) |
| 265-325 | 85 | 47 | 38 |
| 325-330‡ | (2) | | (2) |
| 330-390 | 72 | 47 | 25 |
| 390-395‡ | | | (-) |
| 395-455 | 53 | 47 | 6 |
| 460-520 | 52 | 47 | 5 |
| 525-585 | 47 | 47 | — |
| Body surrounded by oxygen | | | Total 1076 |
| 595-655 | 46 | | |
| 660-720 | 33 | | |
| 725-785 | 34 | | |
| 790-850 | 24 | | |
| Body surrounded by air | | | |
| 855-905 | 48 | | |

* Lung rinsing period. Estimated value of nitrogen elimination for this period.

† Diffusion of nitrogen into system includes atmospheric nitrogen diffusing through rubber tubing, helmet, spirometer water seal, and nitrogen diffusing through the skin.

‡ Represents a period of lung rinsing whenever a shift was made in spirometer systems. Nitrogen elimination values estimated for these periods.

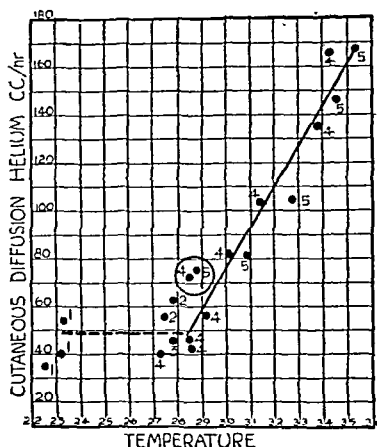


Fig. 9—Cutaneous diffusion of helium in relation to temperature, measured as cubic centimeters of helium recovered from the lungs per hour when the body is immersed in a helium atmosphere, pressure 700 mm. The numbers 1 to 5, refer to different subjects. The encircled values were obtained after the previously heated ambient helium had been cooled to 29° C. (From Behnke and Willmon, *Am. J. Physiol.*, 1940-41, 131:627.)

periment following the prolonged inhalation of oxygen and when the body appeared to be nitrogen free, the substitution of oxygen for the ambient air in the bag brought about a sharp reduction in the quantity of nitrogen recovered from the lungs amounting to about 10 to 20 cc. per hour, Table III. This quantity of nitrogen, however, is only one-third to one-fifth the amount that one would expect to recover were diffusion sufficiently rapid to establish equality between the pressure of ambient nitrogen and its pressure in the skin and subcutaneous vessels.

The rapid diffusion of helium indicates the cutaneous penetration of gas. In experiments when helium was breathed, it was possible to recover from the lungs only about two-thirds of the helium, estimated on the basis of solubility in fluid and lipid constituents, to be present in the body following saturation in a helium atmosphere. Further, the demonstration that helium diffuses rapidly from the urine contained within the bladder walls of divers subjected to rapid decompression from high pressure, suggested that the outward diffusion of helium through the skin accounted for the one-third or greater discrepancy between the pulmonary measurements and the estimated helium content of the body.

If the subject breathes air or oxygen in a hood and the body is surrounded with helium, then a constant volume of helium will be excreted by the lungs after 30 to 60 minutes, provided that the temperature of the gas in contact with the skin is controlled.

In Figure 9, the relationship is apparent between the helium collected in the spirometer and the temperature of the ambient helium in the bag surrounding the subject's body. The abrupt linear rise in the amount of gas diffusing through the skin in the range of 28°C ., and upward is explained chiefly on the basis of increased cutaneous blood flow. There is in fact a close correspondence between the computation of peripheral blood flow on the basis of heat loss from the body as demonstrated in the calorimeter, and on the basis of diffusion of helium through the skin. In contrast with nitrogen, the diffusion of helium is so much greater that equality appears to be established promptly between the pressure of the ambient helium and its pressure in the skin and underlying blood vessels.

3. *The Helium Elimination Curves.*—If the nitrogen that is carried away from the tissues after the first 40 to 60 minutes of oxygen inhalation has its depot in fatty tissue then helium possessing a low fat solubility coefficient should be eliminated faster and in smaller quantities during a corresponding period of time.¹² Following exposure in a helium-oxygen atmosphere it is observed that the absorbed gas leaves the body in about one-half of the time required for nitrogen removal and that the plotted data, Figure 8, resemble the nitrogen curves characteristic of the dog. The amount of helium both in percentage of the body total and the actual quantity eliminated after the first hour are small compared with nitrogen. During exercise sufficient to increase oxygen consumption threefold, almost all of the helium was eliminated during the first 15 minutes, and after 40 minutes 90 per cent of the helium had left the body.

4. *The Field Test of Decompression.*—There is yet a better way to demonstrate the difference in the capacity of fat to absorb nitrogen compared with helium. In diving operations and caisson work the length of time required for decompression is a good index of the quantity and rate of removal of gas absorbed in the tissues.

Although about 75 per cent of the total body nitrogen is given off at a comparatively rapid rate in depths up to 100 feet, and hence does not usually contribute to the development of "bends," there appears

TABLE IV

COMPARISON OF TOTAL DECOMPRESSION TIME FOLLOWING
EXPOSURE IN COMPRESSED AIR AND EXPOSURE
IN A HELIUM-OXYGEN ATMOSPHERE

| <i>Depth</i> | <i>Exposure</i> | <i>Recompression*</i> | |
|--------------|-----------------|-----------------------|----------------------|
| | | <i>Air</i> | <i>Helium-oxygen</i> |
| <i>ft.</i> | <i>min.</i> | | |
| 90 | 100 | 50 | 75 |
| 90 | 180 | ... | 77 |
| 90 | 360 | ... | 79 |
| 90 | 540 | 638 | 79 |
| 150 | 80 | 141 | 121 |
| 150 | 180 | ... | 126 |
| 150 | 360 | ... | 128 |
| 200 | 65 | 217 | 154 |
| 200 | 90 | ... | 164 |

* Time in minutes.

to be a relatively small amount of gas dissolved in the fat of bone marrow and in the spinal cord that requires many hours for removal. Following an exposure of 9 hours (probable saturation) in compressed air simulating a depth of 90 feet, a period of $10\frac{1}{2}$ hours was required for decompression. On the other hand, a 2-hour exposure (75 per cent saturation) at the same depth required only 60 minutes for decompression. In tissues other than bone marrow and the spinal cord, gaseous diffusion and a greater circulation of blood tend to equalize nitrogen pressure throughout the body. Are the greater nitrogen uptake, the limitation of diffusion by bony walls, and the sluggish, sinusoidal circulation the factors responsible for the slow decompression necessary after long exposures in compressed air?

By contrast, the properties of helium render this gas ideal for diving and the decompression time following saturation in a compressed helium-oxygen atmosphere is not only greatly reduced but no appreciable decompression is required in excess of one hundred minutes' exposure as shown in Table IV. With reference to helium, the period of

decompression of 79 minutes stands in contrast with the corresponding period of $10\frac{1}{2}$ hours required for air. Thus, the test data obtained from rapid decompressions corroborate the laboratory analysis as to the contrasting behavior of nitrogen and helium.

III. PHYSICAL QUALIFICATIONS FOR WORK IN ABNORMAL PRESSURES

1. *The Altitude Tolerance Test.*—The selection of individuals resistant to “bends” and other ills incident upon decompression has been difficult. *A priori*, one might select men devoid of excess fat since every kilogram of adipose tissue absorbs 52 cc. of nitrogen per atmosphere of pressure. A second important consideration, in view of the manner of gas transport, would be circulatory efficiency in the sense of good cardiac output and adequacy of collateral circulation. Degree of cardiovascular tone and age therefore would appear to be important criteria. Yet susceptibility to “bends” could not be predicated on the basis of these qualifications alone. Essentially it was necessary to know for each individual his resistance to the ill-effects of decompression by means of a specific test.

To meet this practical need, individuals were exposed to an atmosphere equivalent to a depth of 100 feet for a period of 28 minutes. The subsequent rapid decrease in pressure to normal during a period of 2 minutes induced symptoms in susceptible individuals but the test had obvious disadvantages in that, not only was an undetermined quantity of nitrogen absorbed during the 28-minute period of exposure that fell far short of saturation, but symptoms elicited by the test required recompression treatment.

These disadvantages were overcome by an experiment in which the normal barometric pressure was decreased rapidly in what may be termed an altitude tolerance test.¹³ The simulated altitudes to be reached range from 30,000 to 40,000 feet at a rate of ascent of 5,000 feet per minute, and the duration of stay at the designated altitude is one hour unless aeroembolism supervenes. Oxygen was breathed continuously in these tests.

The results of sixty tests indicated that twenty-eight divers and aviators were able to remain free from symptoms at or above an altitude of 34,000 feet. On the other hand, thirty-two divers and aviators developed “bends” and occasionally incipient asphyxia. The lowest altitude at which symptoms occurred was 27,000 feet. Areas of old injury

proved to be frequent sites for the location of the characteristic pain associated with "bends." This test has served to classify aviators as to their ability to remain free from symptoms at altitudes above 30,000 feet, and deep sea divers as to their resistance to compressed air illness. The divers, for example, who descended to depths of 440 feet in search of a disabled submarine, and ascended safely to the surface, were men who were able to remain free from symptoms for a period of one hour at a simulated altitude of 40,000 feet.

2. *The Specific Gravity of the Body as an Index of Obesity.*—Our problems as analyzed in this lecture are intimately concerned with the amount of fat in the body. Measurements of the nitrogen dissolved in the tissues yield data which may be used to estimate fat content but the procedure is too tedious for routine determinations.

A direct method that serves effectively is the measurement of the specific gravity of the body as a whole, essentially a determination of the density of corporeal tissue in relation to unit volume.^{14,15} This objective is attained by weighing an individual in air and in water. The relationship between the loss of weight in water and the weight in air is an index of the density of the tissues. The influence of fat, possessing as it does the lowest density of any body constituent, is apparent.

It is not necessary to go into details as to procedures. It suffices to state that the proper method, taking due care to measure the residual air volume, has enabled us to classify men as to their degree of obesity on the basis of the outlined principles. Fat men tend to float in water and values in the range of 1.030 for specific gravity are characteristic of these individuals. On the other hand, for a group of lean men in the Naval Service, average weight 150 pounds, the mean specific gravity was 1.080. For a group of professional football players, although their weight was 200 pounds, the mean specific gravity was also 1.080 ± 0.001 . This fact tends to show that it is the inherent composition of tissue rather than the absolute weight that governs specific gravity.

3. *The Composition of the Human Body.*—It has been helpful in the study of the effect of the abnormal pressure environment on the individual to consider the body as a mass of essential tissue separate from the excess fat. In the completion of our analysis various fragments of knowledge can be assembled into a mosaic that reveals the composition of the true body mass as relatively constant under controlled conditions for individuals of the same sex and age groups, realizing that eventually

TABLE V
COMPOSITION OF THE BODY

| Substance | Specific gravity | Water | Solid constituents | | Basic body composition equivalent combinations sp. gr. 1.099+0.001 | |
|---------------------|------------------|----------------|--------------------|------------------|---|-----------------------------|
| | | | Percentage | Specific gravity | Substance | Percentage |
| Blood | 1.060 | Per Cent 80 | 20 | 1.4 | | |
| Tissue | 1.060 | 80 | 20 | 1.4 | {Tissue Bone Fat | 75.0 15.0 10.0 |
| Bone | 1.56 | 30 | 70 | 1.68 | | |
| 0.5 { Calcium salts | 3.00 | | | 3.0 | {Tissue Bone salts Fat | 82.5 7.5 10.0 |
| 0.5 { Tissue | 1.060 | 80 | 20 | 1.4 | | |
| Fat | 0.94 | | | | {Water Solids Bone salts Fat | 66.0 16.5 7.5 10.0 |
| Body as a whole | 1.099 | 66 | {16.5 7.5* | {1.4 3.0 | {Water Solids Fat | 66.0 24.0 10.0 |

* Calcium salts in bone.

quantitative analyses will define the range in variation of such constituents as bone and fluids.

The true weight of the body, therefore, as represented by Figure 1, is assumed to consist of 15 per cent bone, 10 per cent essential lipids, and 75 per cent tissue. The specific gravity of this mass then can be computed on the basis of the following data:

Bone is frequently analyzed as containing 50 per cent mineral substance, largely calcium salts to which a specific gravity value of 3 may be assigned. The other half of bone amounting to 7.5 per cent of the body weight may be classed as tissue.

The specific gravity of the lipids is of the order of body fat, 0.94, a value obtained experimentally on the basis of actual fat loss in relation to specific gravity.

For tissues a value for specific gravity of 1.060 is the same as that obtained by repeated determinations of whole blood withdrawn from the above mentioned test subjects. Analyses for individual tissues ac-

TABLE VI

EFFECT OF EXCESS FAT ON THE SPECIFIC GRAVITY OF THE BODY

| Basic composition | Weight units | Volume units | Specific gravity | Specific gravity determinations of 174 Naval personnel | | |
|--------------------------|--------------|--------------|------------------|--|---------------------------|--|
| | | | | No. men | Range of specific gravity | Difference thoracic, abdominal circumference |
| Tissue | 75.0 | 70.75 | | | | |
| Bone | 15.0 | 9.62 | | | | |
| Essential lipids | 10.0 | 10.70 | | | | |
| | 100.0 | 91.07 | 1.099 | 21 | 1.090—1.099 | 7.2 |
| 10 per cent excess fat | 100.0 | 91.07 | | | | |
| | 11.1 | 11.82 | | 30 | 1.080—1.089 | 6.3 |
| | 111.1 | 102.89 | 1.080 | 41 | 1.070—1.079 | 5.5 |
| 20 per cent excess fat | 100.0 | 91.07 | | | | |
| | 25.0 | 26.60 | | 41 | 1.060—1.069 | 5.2 |
| | 125.0 | 117.67 | 1.062 | 31 | 1.050—1.059 | 4.3 |
| | | | | 5 | 1.040—1.049 | 4.2 |
| 33.3 per cent excess fat | 100.0 | 91.07 | | 3 | 1.030—1.039 | 0.9 |
| | 50.0 | 53.76 | | 2 | 1.020—1.029 | -0.1 |
| | 150.0 | 144.83 | 1.036 | | | |

according to Vierordt,¹⁶ give values of the order of 1.014 for pericardium to 1.1219 for tendon; e.g., muscle, 1.051, brain, 1.040, liver, 1.057. For tissue it may be assumed that the distribution of water and solid constituents is in the ratio of 80 to 20. In accord with this distribution the specific gravity of the solid residuum is 1.40.

The analysis of the composition of the body is summarized in Table V, showing the values used for blood, tissue, bone, fat, and solid constituents. The basic composition of the body can be analyzed in several ways as long as the ratios of the constituent substances or their equivalents are not altered with respect to body weight. The same value for specific gravity of 1.099, representing the true body mass, is therefore applicable to any group arrangement of constituent substances, as shown in the table.

If to the true corporeal structure, excess adipose tissue be added in percentages of 10, 20 and 33.3 of the total body weight, the respective values for specific gravity will be 1.080, 1.062, and 1.036 corresponding

TABLE VII

BODY COMPOSITION AND SPECIFIC GRAVITY OF A DEEP SEA DIVER
COMPUTED FROM THE GASEOUS NITROGEN CONTENT OF THE BODY
(See Table III, Page 576)

| | | | |
|---|----------------------|----------------|-------------|
| Body weight | = 70 kg. | Total nitrogen | = 1,076 cc. |
| Weight fluids | = 70×0.60 | | = 42 kg. |
| "Water" nitrogen | = 42×9 | | = 378 cc. |
| "Fat" nitrogen | = $1076 - 378$ | | = 698 cc. |
| Weight fat | = $698 \div 52$ | | = 13.4 kg. |
| True body weight | = $10/9 (70 - 13.4)$ | | = 63 kg. |
| Excess fat | = $70 - 63$ | | = 7 kg. |
| Weight water | | | |
| Ratio— | | | = 66.6 |
| True body weight | | | |
| <i>Corrections—</i> | | | |
| Water, $0.66 \times$ true body weight | | | = 41.58 kg. |
| "Water" nitrogen = 4.58×9 | | | = 374 cc. |
| "Fat" nitrogen = $1076 - 374$ | | | = 702 cc. |
| <i>Specific gravity of the body, computed—</i> | | | |
| True body weight | Weight (units) | Volume (units) | |
| Water | 41.58 | 41.58 | |
| Fat | 6.30 | 6.77 | |
| Solid constituents | 15.12 | 9.00 | |
| | 63.00 | 57.35 | |
| SPECIFIC GRAVITY = $63 \div 57.35$ | = | 1.098 | |
| True body weight plus excess fat = $63 + 7 \div 57.35 + 7.53$ | | | = 1.079 |
| Specific gravity of the diver's body as determined by the method of water displacement | | | = 1.060 |

to the division of Naval personnel into three groups on the basis of high, intermediate, and low specific gravity measurements.

On the basis of determinations of specific gravity the value of 1.099 is higher by two units than the top figure obtained in a series of 200 tests in which healthy individuals between the ages of 20 and 40 served as subjects. Men possessing the highest values therefore have no excess fat and their bodies contain only about 10 per cent by weight of lipid matter that is regarded as essential. A reading for specific gravity of 1.080, or approximately the average for the high group, is indicative of the presence of 10 per cent *excess* fat, a figure of 1.062 indicates the presence of 20 per cent *excess* fat, while a value of 1.036 obtained on several fat men denotes that 33.3 per cent of the body weight consists of *excess* fat, Table VI.

The analysis applicable to the diver whose nitrogen measurements extended over a period of 15 hours, Table VII, summarizes the results with reference to the estimation of the fat content of the body both on the basis of measurements of nitrogen elimination and determination of specific gravity. In this particular example some discrepancy exists between the specific gravity as measured, and the specific gravity as computed on the basis of excess fat in relation to basic body structure. But undoubtedly quantitative data obtained in the future as to the relative amounts of the constituents in the true body mass will diminish the difference.

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SURGICAL TREATMENT OF PERIPHERAL EMBOLISM AND ANEURYSM *

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FROM the first World War sufficient experience in the treatment of wounds and diseases of the vascular system was derived to form a basis for the treatment of lesions of this system. With our entrance into the second and greater World War the practical application of these principles will be put to the test in an immediate and wide field. In the treatment of peripheral embolism and aneurysm these principles must be used. An enumeration and discussion of them is even more timely than it was thought when the subjects were presented at the Graduate Fortnight. While many of the principles arising in the treatment of both of these conditions are similar, they will be discussed separately for clarity.

I. PERIPHERAL EMBOLISM

In arterial embolism there is a sudden and complete closure of a major vessel. Shock is inevitably present and, unless therapeutic efforts are successful, the loss of the limb and, in a high percentage of cases, the life of the individual results. The final closure of a vessel already chronically occluded is another picture, because in such chronic closures collateral circulation channels have already been prepared. Surgical treatment of peripheral embolism until recently—and unfortunately in some places still—has been confined to major amputation, if the patient survived until demarcation was complete. Fortunately, surgical therapy has been proven sufficiently successful so that a fair percentage can be saved, not only from death, but from the previous major amputation.

Peripheral embolism is accompanied by a left side heart disease in four out of five instances. Usually there is the added insult of auricular fibrillation, severe infection or an operative procedure. The paradoxical occurrence of an embolus from the right side of the heart or the peri-

* Delivered October 17, 1941, at the Graduate Fortnight of The New York Academy of Medicine.

TABLE I
SITE OF PERIPHERAL EMBOLI

| <i>Site</i> | <i>Rate of Occurrence</i> |
|-----------------|---------------------------|
| Aorta | 4.5 |
| Iliac | 17.3 |
| Femoral | 54.5 |
| Popliteal | 11.3 |
| Arm | 12.1 |
| Tibial | .5 |

pheral venous system requires a patent foramen ovale. In arterial disease a local trauma may loosen a plaque which becomes an embolus, but more often this results in thrombosis.

Symptoms: *Pain* is inevitably present and it is sharp and severe. *Tenderness* follows the embolus and is greatest at the site of its lodgement. The *color* of the limb changes to a white, dead-like appearance, followed by a blotchy discoloration and eventually gangrene. The *reflexes* are absent and there is a paralysis of the part. With the *color change*, the part becomes *cold*. Oscillometric readings and blood pressure are zero.

Differential Diagnosis: If there is a diseased heart, which is fibrillating and has an added strain with the symptoms already enumerated, a diagnosis of embolus is indicated. *Arterial thrombosis* must be differentiated. In arterial thrombosis there is evidence of failing arterial circulation for some time and arteriosclerotic changes in other vessels, either by palpation or x-ray examination. Occasionally the differential points are not clear until operation time. *Acute thrombophlebitis* should not be difficult to differentiate, as in this condition the foot is warm, enlarged and cyanotic with distended veins. There is normal arterial circulation as shown by palpation and oscillometric readings.

Pathology: At the site where the embolus lodges in the intima an inflammatory process develops. There is swelling of the walls of the vessels and later destruction of the intima. The embolus usually lodges at the bifurcation of an artery, where the lumen of the vessel rapidly becomes smaller. The most common site is at the bifurcation of the femoral and femoral profunda arteries, the internal and external iliac, the bifurcation of the abdominal aorta and the division of the anterior posterior tibial arteries (Table I).

Spasm of the involved vessel and the collateral vessel is invariable and may be a factor in the pain (Lund, McKettrick and Allen). This spasm has a physiological basis, as it prevents the formation of a thrombus below the embolus site. If this spasm is relaxed before adequate therapeutic measures have been instituted, the entire vessel below the embolus may be entirely closed. Occasionally the spasm of the collateral circulation will relax sufficiently to permit a degree of circulation to be established around the embolus. Thrombosis occurs in 50 per cent of patients with an embolus. This is one of the reasons for doing early embolectomy, as other conservative measures are unable to restore circulation when the thrombosis is present. There is a definite difference between the closure of a major artery by an embolus and by a ligation. Halstead in 1924 was unable to find gangrene occurring from ligation of the subclavian artery and Mulvihill reported an incidence of only 14.7 per cent gangrene in sixty-seven ligations of the common iliac, external iliac and femoral arteries. Wolf found that 50 per cent of the ligations of the common iliac artery resulted in gangrene, while only 15 per cent of the ligations of the popliteal arteries affected the circulation. In the arm a mere 5 per cent of the brachial artery ligations were followed by gangrene. In a ligation of an artery the collateral circulation is frequently adequate. After embolus, however, the thrombus which frequently forms, extends into collateral branches and prevents their function, even if spasm can be relieved.

Treatment: The names of the surgeons who first tried embolectomy are those whose surgical work has been outstanding. Abanejew performed the first exploration for peripheral embolus in 1895, but failed to locate one. Moynihan, in 1897, removed an embolus from the popliteal artery, but the patient died. In 1907 both Stewart and Doberauer removed emboli with temporary benefit, but thrombosis followed shortly thereafter. Trendelenburg's first effort on pulmonary embolism was in 1907, the patient dying of hemorrhage on the table. In 1908-09 Proust, Schussi, Murphy, Carrel and Leriche all tried the operation with failure. The first successful embolectomy (Lahey, in 1911) was followed shortly thereafter by Key in Sweden. From 1911 to 1925 nearly all of the operations of this type were done in the Scandinavian countries and the procedure was neglected by surgeons in other countries. While there had been 150 cases in Scandinavia up to 1927, there had been less than twenty reported in the United States, Canada and Eng-

land. Since that time there have been many successful operations with the Scandinavian figures of 382 embolic operations leading all the others.

While an occasional patient will survive without the removal of the embolus, we believe embolectomy is indicated in every instance when the diagnosis is made. We base this on the fact that we have been able to remove not only the embolus, but the accompanying thrombus in a high percentage of patients if seen within a reasonable time. Conservative measures advocated, such as the suction pressure boot, may play a part occasionally. Our experience has been that many of the patients who survived without operation did not have true embolisms, but rather arterial thromboses or the final closure of a vessel previously constricted by arterial disease, the previous constriction permitting and stimulating adequate collateral development. We have seen patients develop gangrene and eventually die with a suction pressure apparatus and in one patient the entire epidermis sloughed during such a treatment.

Surgical Technique: Local anesthesia should be employed exclusively and adrenalin, a severe vasoconstrictor, should not be added. These people are in poor condition and a general or spinal anesthetic is often too great a load for their circulatory system. Gentleness is of the utmost importance in this procedure. The incision is made over the femoral canal, just below the inguinal ligament for femoral, aortic or iliac embolus, and a vertical incision gives the best exposure. The femoral artery is isolated in the wound and a tape passed around either end of the exposed artery. A fine silk stay suture is placed at either end and a longitudinal incision made in the artery. If a thrombus is present, it is teased out with a smooth forceps from the distal end first. With a soft rubber catheter preventing the passage of clots below the incision, the proximal end is then removed. Frequently the thrombus breaks away from the embolus, which remains attached in the lumen. A wire corkscrew instrument may be inserted up the artery to dislodge the embolus. In order to protect the intima, it has been my practice to protect the corkscrew by a rubber catheter as it is introduced. The catheter may be withdrawn when the obstruction is reached. Usually the embolus begins to pass when the corkscrew is withdrawn, but no one instrument is always successful and some ingenuity is necessary. Suction applied to rubber or ureteral catheters may be effective in loosening the clot and on occasion we have borrowed many instruments from the urological and bronchoscopic departments, including the minute biopsy and flexible

foreign body instruments. In the femoral area it is advisable to expose the profunda to be sure its function is not impaired. The technique must be adjusted according to the pathology present. In one instance, Carter¹ was able to guide a femoral embolus into a profunda branch manually, thus reestablishing the femoral circulation without the necessity of entering the arterial lumen. There must be free flowing, spurting blood, and when this does not occur, it indicates that there is still some obstruction and further efforts must be made to free the artery. In some cases incision can be continued through the inguinal ligament and the hand passed retroperitoneally along the large vessels to the bifurcation, and the vessel milked manually. Considerable blood spurting should be permitted to be sure that all fragments and clots have been removed.

In the presence of bilateral symptoms both femoral arteries are exposed at once. By lightly constricting the artery of the other side below the incision site, the possible passage of a clot into the opposite periphery can be prevented. For the same reason, even when only one side is involved, the pulsation of the foot on the unaffected side should be watched most carefully after the clot has been removed.

The artery is closed with fine arterial silk on minute curved needles, the sutures being placed so they do not enter the intima. Oversuturing should be guarded against. One should remember that the pressure at any point in the arterial wall is inversely proportional to the velocity of the blood flow and that a single running suture is often sufficient to prevent bleeding. Carrel and Key advocated coating sutures, needles and instruments with vaseline, but this technique has been found cumbersome and unnecessary. The needles slip and the delicacy of technique required for this type of surgery is too often sacrificed.

Irrigation of the artery with 25 per cent heparin solution at the time of operation is a recent addition to the technique. It seems to be helpful and probably has prevented formation of some immediate thromboses.

After Care:

1. *Heparin:* Heparinization is a definite adjunct to arterial surgery. It should be used routinely after operation. One must temper the continuous drip technique with patients whose cardiac status would not stand the continuous overloading of the venous system. In those cases, the clotting level may be maintained below normal by 5 cc. given every two or three hours. Dicoumarin, presented and discussed by Dr. Irving

S. Wright, at this same meeting, no doubt will play its part in making arterial surgery safer in the future.

2. *Perivertebral sympathetic nerve block*: Perivertebral nerve block after embolectomy is important. With the removal of the embolus and accompanying thrombus, the introduction of 5 cc. of 2 per cent novocaine into each of the lower dorsal and lumbar sympathetic ganglia relaxes the spasm and stimulates circulation, not only in the major vessels, but in the collateral circulation.

3. *Care of the limb*: The limb should be protected from bruising or skin breaks and should be kept warm, but not burned. It is best to wrap the foot in candy cotton and put it in a large cradle where the temperature is controlled between 88° and 94° F. Elevation of the leg is contraindicated but the oscillating bed with its gentle arterial massage, is helpful.

4. *Drugs*: After embolectomy the smooth muscle relaxers may play a part. Papaverine, atropine, and pantopon may be given as often as every two hours. Whiskey is also helpful at this stage.

5. *Exercise*: No effort should be made to make this leg carry weight until it has been shown that the circulation is intact. The cardiac status in most cases delays the attempt in walking until this prerequisite has been satisfied.

Should a second embolus occur it may also be removed. Cases have been reported in which as many as three consecutive embolectomies have been performed with recovery (Macfarlane). In a review of all the patients who were seen at the Post-Graduate Hospital between 1930-39, the difficulties of the differential diagnosis between embolus and thrombosis were observed. Rejecting certain doubtful cases in which the cardiac status was considered primary, twenty-six patients were described, of which twelve were operated and five survived—a percentage of 41.6 per cent. Of those who survived without operation, all lost their limbs. Again, the possible error in diagnosis of many of this latter group must be emphasized. Personal observations have been made on sixteen patients with true emboli, twelve of whom have been operated and four of whom were not operated. Dr. Franklin Carter, of the Post-Graduate Hospital, has had seven such patients, several of whom I have also observed. Of the total patients operated, thirteen have had the circulation restored. While the percentage of patients living today after this procedure is only 23 per cent, this figure can not be taken as a

true one for embolectomy success. It is actually 61.5 per cent, because it must be recognized that if embolectomy restores circulation it has been successful. Embolectomy can not be expected to prevent death from an advanced heart lesion or to prevent other phenomena. These patients die from the lesion causing the embolus, not from the embolectomy. If embolectomy is not performed, the death rate is higher from the gangrene which they usually develop or from the operation for the gangrene. This has been proved by many workers. I observed five patients who were not operated on, who developed gangrene and died. If such patients do have spontaneous recoveries, without operation, they are permanent vascular cripples. One such patient seen in the clinic recently recovered spontaneously, but now has zero oscillometric readings and such inadequate collaterals that amputation seems almost inevitable. One should not be discouraged by the low percentage of patients living five years after their operation. Were this same outlook carried to the field of cancer or brain surgery, many patients now cured of these lesions would be dead.

The end results in the embolectomies in Sweden showed that one quarter die in one year, one-half are dead in three years, one-third are alive in five years and one-eighth are alive in ten years. The graph is practically identical with that of those living after excellent surgical and x-ray therapy for cancer of the breast. This seems sufficient answer to those surgeons who have stated that the operation is useless, because of the poor risk of the patient group. Certainly no one would advise against operation for cancer of the breast merely because only one-eighth of the patients will survive ten years.

One of our patients operated sixty hours after a large saddle embolus of the abdominal aorta had been lodged, is alive today with complete circulation in one limb and in the other limb to the knee. This patient was operated on, at the instance of the family, in a condition of extremis, with a temperature of 104° . It was their contention that the patient who was a minister, would survive the procedure because of his profession, if given surgical help. Emboli from both sides were removed with considerable difficulty with restoration of circulation in one leg and improvement of circulation in the leg which was already gangrenous to the middle of the calf. This is illustrative of the factor so well outlined by the late Osler, whose precept of never letting a person die of one disease merely because he has another, is frequently forgotten by us today.

The recovery of this patient and other less dramatic recoveries have convinced us that no arbitrary time limit, as to whether to operate or not, can be placed on these patients. It is our intention to operate on all of them as soon as we see them and we believe that more people with emboli will be alive in the next ten years than have survived in the past.

II. ANEURYSM

Diagnosis, symptoms and treatments of peripheral aneurysms vary greatly with their site and, because of that, only general therapeutic suggestions can be given. While we define aneurysm as a sac filled with blood communicating with an artery, its subdivisions, as contained in the text books, number twenty-five. For clarity I will subdivide the peripheral aneurysms as follows:

Peripheral Aneurysm

I. Arterial

Acquired

1. Result of trauma
2. Result of degenerative disease

Congenital

II. Arteriovenous

Acquired

1. Result of trauma
2. Result of degenerative disease

Congenital

I. Arterial Aneurysm: In arterial aneurysm we have a weakness of the wall of the vessel due either to an increased arterial pressure or a traumatic or degenerative lesion of the vessel wall or a combination of both of these factors. The sac which develops has a neck through which it communicates with the main vessel and the contents of the sac are liquid and coagulated blood in various stages of resolution. The wall of the sac will be of the so-called true or false aneurysmal type. In the former the weakened arterial walls are pushed ahead by the dilatation and in the latter, the walls of the vessel are destroyed and the sac is made up of surrounding tissues with only an endothelial lining. There may be efforts to strengthen the wall by the proliferation of fibroconnective tissue in either of these forms, but this fails eventually because of the force of the blood which at times is sufficiently strong

to erode cartilage and bone. The clots are white at the periphery and red at the center with many degenerative changes occurring in them. The older ones become calcified.

Symptoms: While all aneurysms form a *tumor*, the contiguous structure, particularly where the aneurysm is small, may hide it. An *expansile pulsation* is present in the early aneurysm, but with further clot elimination, the pulsation may be transmitted or even obliterated. *Pain* is a variable symptom, depending upon the structure which is being compressed by the growing tumor. In the extremities this may be a negligible factor, although in the popliteal aneurysms pain and weakness of the muscles supplied by the sural nerve may be an early sign. The *pulse* is weak or absent distal to the aneurysm. This applies also to the oscillometric readings and blood pressure. Paré's bruit, which is present in early cases, depends on the clotting. When present, it is of the rough systolic type. In addition, in the acquired type there will be a scar at the site of injury. The congenital aneurysms at times are multiple.

Treatment: 1. The ideal treatment of either acquired or congenital aneurysms is excision and end-to-end anastomosis of the vessel. This is more often possible in the traumatic type than is generally supposed. We have performed this operation successfully four times in the last year. The artery is exposed, the aneurysm excised and the arterial ends sutured with interrupted and continuous fine arterial silk, after which the suture line is reinforced with nearby muscle or fascia. By release of the vessel from its bed and flexion of the joint a defect of 4 to 5 cm. may be closed. This point can not be overstressed in war surgery, where laceration or division of an artery is frequently considered sufficient cause for the amputation of the involved extremity.

2. *Obliterative Operative Procedures:* The reapplication by Matas of the ancient conceptions of Philagrius of obliterating the involved vessel is the treatment of choice in many of these patients. The circulation is controlled above and below the aneurysm sac, the sac then widely opened, its contents of debris, clots and necrotic material evacuated and each collateral opening into the sac closed by sutures. The major arterial openings are ligated and then sutured from within. The sac is obliterated by multiple layers of sutures without excising the sac. A large muscle transplant aids in obliteration. In the popliteal space we have used the gastrocnemius and the popliteus muscles most successfully. In some of the smaller ones muscle transplants are not required. There is a good

deal of misconception about the principles of this operation even in the minds of well trained surgeons. The principle is to obliterate, *not remove*, the sac. To remove the sac one must do irreparable damage to the extremity. Excision of an aneurysm of this type frequently results in gangrene.

3. The most successful type of reconstructive operation on the artery is the use of a vein transplant. A rather large vein must be selected and sutured to the ends of the artery to bridge the defect. The incidence of thrombosis, which so frequently attends such an operation, can be decreased by heparin and Murray has shown many well functioning vein transplants years after their introduction. Babcock^{2,3} in his carotid jugular anastomoses, demonstrated how well a vein can accommodate the arterial blood. The large jugular vein, when united to the smaller carotid artery, shrinks down to the size of the arterial column, and after a time its wall becomes as thickened as the artery. This operation will have its place many times in the repair of the injuries resulting from the present world conflict.

4. The modifications of the original Matas⁴ procedure of opening the aneurysm and plastically repairing the wall over a tube or other foreign material has been accomplished in selected instances, but an arterial wall once so seriously damaged as to stretch into an aneurysm may weaken again. The use of an absorbable material over which to suture, such as glucose, is of only experimental interest at the present time. Experiments are likewise being made with the use of other foreign matter such as talcum powder and cellophane which cause peri- and endoarteritis. It has been shown that these and other similar materials cause inflammation and fibrosis to a marked degree and it may be possible to take therapeutic advantage of this fact. One operation of this type has recently been performed by us.

In any type of treatment of aneurysm where the main vessel is or may be occluded, it is most important that stimulation of collateral circulation be continued. Antispasmodic drugs, whiskey, external heat and avoidance of all trauma are all valuable agents. Lumbar sympathetic nerve block has its place in relaxing spasm. All strain on the part must be avoided until there is proof that adequate circulation is established and in cases where the small collaterals are carrying the circulation the patient must be restricted physically within the limits of his arterial supply.

II. Arteriovenous Aneurysm:

Acquired Arteriovenous Fistula: The most common cause for the acquired type of arteriovenous aneurysm is gun shot, stab or airplane and automobile injuries. A large percentage of them follow war wounds. The arterial blood rushing into the sac or vein causes definite physiological changes. They are as follows:

Physiological Changes Following Arteriovenous Fistula

1. A blood pressure fall with recovery, but greater pulse pressure
2. An increased pulse rate.
3. An increased venous pressure
4. Increased cardiac output (depends on size and location)
5. Temporary decrease in size of heart and artery, then dilation with hypertrophy of the heart
6. Increased total blood volume
7. Collateral circulation around fistula

The degree to which these changes occur depends upon the size of the vessel involved and the length of time the abnormal communication has persisted. If the communication is at all large, its closure is imperative to prevent changes and eventually the cardiac failure which results. The symptoms in the acquired type of aneurysm are usually so apparent that diagnosis is evident. The scar at the site of the injury, followed by enlargement, dilation of the veins of that extremity, increased temperature and a bruit are confirmatory. The Paré sign of decreased pulse rate with pressure over the fistula will be present, as will a diminished pulse and blood pressure and oscillometric readings distal to the fistula. An arteriogram is confirmatory. Pain depends upon the extent of the pressure on the nerve or sensitive parts. All symptoms following venous congestion, such as pigmentation, dermatitis, ulceration, edema, hemorrhage or even gangrene may be present. A higher oxygen content in these veins than in the normal vein, due to the arterial flow is another confirmatory test.

Pathology: The connection is lined by endothelium and at times clots develop in the sac. The venous blood, driven back by arterial pressure during systole, may enter the artery during diastole. Arterial blood returns through the nearest venous channels and starvation of the periphery may result.

Surgical Treatment: It is wise to postpone operation until four to

six months after the development of the fistula to permit the sudden physiological changes accompanying the fistula to have reached a level and, more important, to permit collateral circulation to become adequate. At the time of the repair, the physiological changes previously mentioned must be considered, as the closure of the fistula causes an exact reverse of all the points mentioned. If the fistula has been present for a long time, it may be necessary first to decrease the blood volume by phlebotomy to prevent overstrain of the cardiovascular system. It is preferable to omit the tourniquet when the operation is performed. No one operative procedure can be used for all types of fistulas. The ideal treatment would be one in which the fistulous communication was closed and the continuity of the vessels reestablished, but unfortunately this is rarely possible. The site of the anastomosis should be exposed and explored and tapes applied above and below the fistula. The closing of the upper tape will not result in circulatory failure distally in those cases where the collateral circulation is adequate. Care must be taken to ascertain this at the time of operation. The type of operation to be selected may be one of the following:

1. Repair of the fistula in the arterial wall, through the opened and sacrificed vein. Suture materials should be of the finest arterial silk on non-traumatizing, minute, round needles, such as are used in eye surgery. These sutures should not enter the intima. A section of near-by fascia or muscle makes a better reënfacement than the fistulous sac or vein. The ligation of the vein in these instances appears to be of therapeutic value, compensating for the reduced arterial supply by decreasing the rapidity of the blood return.
2. Ligation, proximally and distally, of the artery and the vein, with excision of the intervening fistula and vessels is frequently the treatment of choice, where collaterals are adequate. In this type of treatment the intervening vessels must be removed or the fistula may recur. This operation is used most often in the upper extremity, head or neck.
3. In some cases it is impossible to remove the fistula, because of possible damage to secondary circulation. Quadrilateral ligation is then performed. The fistulous tract is opened and the clots evacuated, all openings into the fistulous tract closed by fine arterial sutures and the sac obliterated by muscle transplant, imbrication.

cation and plication. The use of this operative principle has saved many limbs which in previous years it would have been necessary to sacrifice.

Congenital Arteriovenous Fistula: Many of the symptoms and signs, as well as the therapeutic measures detailed for the acquired aneurysm apply to the congenital type. In the treatment of congenital arteriovenous aneurysm, however, the cardinal point to remember is that they are usually multiple. All of these multiple connections may not be open and functioning at the same time. This point should be explained to the patient, since multiple operations may be required as a result of this. The etiology of these congenital arteriovenous communications is still under investigation. Arteries and veins anastomose most frequently in the hands, feet and sexual organs, as shown by Hoyer, Krogh and others. In studying the embryological rests frequently demonstrated in the newborn, it is not difficult to conceive of the same failure of closure in the arteriovenous system. They are usually multiple and are found most frequently in the upper extremities. When they appear in the lower extremities, they are often diagnosed as varicose veins with onset first noticed at three to five years of age. The history discloses that the physician consulted at that time advised that nothing be done, as the patient "might grow out of it." Another form of arteriovenous connection is the so-called aneurysmal varix, in which the enlarged varicose veins connect with an artery. This lesion, by no means rare, is also commonly diagnosed and treated as varicose veins with resultant technical complications. The *symptoms* in these congenital type lesions differ with the number, size, duration and position of the communications. Large ones are particularly frequent in the upper extremities, while minute ones may occur on the face, particularly around the eyes and mouth, where the term pulsating hemangioma is applied. A congenital fistula was seen in the neck of a patient of Dr. Irving S. Wright⁵ in which a mass of vessels in the suprahyoid muscle area was fed by the left lingual, external maxillary and inferior thyroid arteries and so many abnormal connections from the right external carotid that it was necessary to extirpate all of the main branches of the left external carotid and the entire right external carotid artery in order to close the fistula. Signs of *thrill* and *bruit* at the site of the fistula and arterial blood in the veins are diagnostic in this type of lesion, as they are in the acquired type of fistula, except that in the congenital fistula they are usually larger.

Treatment: The treatment of the congenital fistulas varies with their size. Many small ones, particularly on the face, may be surgically excised and some of the ones which have been sclerosed with a small amount of solution have never recurred. Radium has helped a few. In treating the large congenital fistulas one must be prepared for an extensive and, many times, a multiple procedure. This multiplicity can not be overemphasized. The operations are best performed without a tourniquet so that the site of bruits can be determined and each one eliminated. The operation of choice in the large lesions is quadrilateral ligation and excision of the arteries and veins involved. At times one must remove vessels which appear necessary to the life of the part, but collateral circulation is present so frequently that most of these limbs will not be lost.

The tendency of these fistulas to invade and spread like malignancies has been noticed, particularly in one of our patients. Matas has reported cases which appeared to metastasize. Amputation in some instances is necessary and indicated. In some of these patients connections closed at the time of the operation will open with the increased arterial pressure. In one instance we closed eleven communications only to have the patient return the following year with five new ones. One must be prepared for such discouraging results and continue with the operations in stages until cure is achieved. While local relief is hoped for, it is to prevent the eventual cardiac collapse that the operation is performed.

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TESTICULAR BIOPSY IN THE DIAGNOSIS AND TREATMENT OF STERILITY IN THE MALE*

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THE persistent absence of spermatozoa from the semen denotes absolute sterility in the male. This condition requires that either no substantial number of spermatozoa is being formed, or that an obstruction or defect exists which prevents the escape of the cells from the seminal tract. Certain clinical guides are helpful in determining which factor is the cause. Thickened epididymes favor occlusion, while atrophic testicles indicate that the germinal epithelium is deficient. It has become increasingly apparent, however, that azoospermia may be associated with genitalia which are normal to external examination. Accordingly, there is a real need for an accurate way to determine whether the lack of spermatozoa is due to aspermatogenesis or occlusion. A correct diagnosis is obviously essential to proper management, for an occlusion calls for reestablishment of the patency of the ductal systems, whereas incomplete spermatogenesis theoretically demands that some agent or set of agents be supplied to motivate spermatogenesis.

It has been said that one good diagnosis is worth ten haphazard treatments. The use of testicular biopsies bears out this adage in the problem of the sterile man. The study of testicular tissue has proven to be a reliable and practical method in accounting for the absence of sperm in the semen, and promises to minimize errors in treatment.¹ The tissue likewise affords a new source of information relative to the histopathology of the human testes and may assist in clarifying some of the fundamental clinical concepts of seminal deficiencies.

The procedure of obtaining the biopsy requires no special skill and entails little discomfort and incapacitation. The genitalia are prepared for operation and a small area in the scrotal skin is anesthetized with

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1 per cent novocaine. An incision is made and carried down through the tunica vaginalis. A pair of ocular palpebral retractors is inserted, and the tunical albuginea is exposed. A small "V" shaped incision is made therein and a minute piece of testicular tissue is excised. Silk or fine plain gut sutures are used to arrest hemorrhage and approximate the layers of the wound. The operation is repeated on the opposite side. A suspensory is applied and the patient is sent home from the operating room. The tissue is fixed in Bouin's solution and sections are prepared in the usual manner.

Two main classes of testicular tissue are found.² The seminiferous tubules may contain either normal or defective germinal epithelium. The degree of cellular activity varies considerably in different tubules in each section, but the general contrast is striking and offers little chance for serious confusion. Several types of defective germinal tissue may be seen. The biopsy specimens from some men with normal sized testicles exhibit spermatid cells which have progressed to the spermatid stage, just short of full maturity. Others have germinal epithelium which is arrested at an early stage of spermatogenesis. A third type have tubules almost devoid of germinal epithelium, and their lumens may be filled with hyaline. A fourth type of abnormal testes is characterized by extraordinary proliferation of fibrous tissue about the tubules. Sections of testes associated with occlusion of the efferent seminal tracts have, in main, well-organized germinal epithelium with many mature spermatozoa.

The clinical usefulness of the biopsies is quite apparent. Active normal spermatogenesis requires no stimulating agents. Complete degeneration of the germinal tissue defies treatment with substances now available. Thus, useless or misapplied therapy is avoided and an approach to rational treatment is made.

The mandates of successful treatment of sterility, however, include more than a mere consideration of the histopathology of the testes. Three essential criteria are involved. They are:

1. The primary cause of the disturbance must be recognized and evaluated.
2. Specific and potent therapeutic agents must be available and assimilable.
3. The end organ must be refractory.

Lack of knowledge of certain important facts concerned with these

three criteria accounts for the generally unsatisfactory state of therapy at this time. It may be appropriate to examine these principles in the light of present developments to evaluate current and future modes of the clinical treatment of impaired fertility.

It is likely that faulty spermatogenesis can be assigned as due to one of four causes. The identity of the particular cause is probably the key to effective therapy.

1. An inherited gametogenic factor may account for sterility in man. As yet there is no clinical proof of this theoretical possibility, but other species furnish notorious examples of this genetic phenomena. The mule, which is a hybrid animal, is always sterile. There is no possibility of revoking chromosome patterns, and treatment is futile.

2. A second cause of spermatogenic failure may be some deficiency disease. This is clearly indicated by the effect of inadequate diets in experimental animals.³ The work of Dr. John MacLeod⁴ has demonstrated the necessity of certain foodstuffs, enzymes, and vitamins to the life processes of spermatozoa. The needs of the germinal epithelium may not be dissimilar to the requirements of sperm.

Subclinical or mild deficiency states are now recognized as established clinical entities, and subsequent investigations may reveal that defective spermatogenesis is linked with an inadequate vitamin supply or, more likely, to a failure to absorb and utilize these and other substances.^{5, 6} The past and present clinical experience with corrective dietary regimes and vitamin medications have not been singularly encouraging. Future advances may reverse present attitudes, and it is possible that certain cases of infertility due to deficiencies will be corrected and cured.

3. There is no doubt that the gonads are intimately linked with the other glands of the endocrine system.⁷ Nearly thirty years ago it was shown that removal of the pituitary caused prompt atrophy of the germinal epithelium. Since then an enormous amount of interest has been displayed in the relationship of the reproductive glands to the other endocrines. The clinical application of endocrine therapy in man has borne far less brilliant results than some of the experimental animal work. There are a number of well authenticated reports which illustrate effective treatment of impaired fertility in men with endocrine products but the failures are far more common than the successes. The deserving skepticism is well understood when it is realized what great

obstacles still remain in therapeutic pathways. Species vary greatly in their responses to endocrine substances so that much of the experimental work on animals and birds cannot directly be transferred to the human with the assumption that it is applicable. We have no simple tests to evaluate or diagnose subclinical or minor grades of endocrinal disorders. The therapeutic products which are available are not specific and probably far below basic requirements of actual need. These and many related problems await clarification before the dreams of a "specific hormone" for spermatic tissue will be available in the same sense that insulin is used for diabetes.

4. A fourth class of disturbances which may alter spermatogenesis may be grouped under the term "constitutional and local disorders." It is evident that the testicles are labile structures and are sensitive to certain generalized alterations of body function. It is known that debilitating illnesses will arrest spermatogenesis. Artificially induced fever will cause transient injury to the germinal layers.⁸ Much speculation is given to the effect of less definite influences such as fatigue, nerve strain, overwork, alcohol and minor illness. It may well be that subnormal semen is much more adversely affected by these factors than are specimens of high quality. These agents may then resolve themselves into individual considerations which have relatively little effect on the very fertile, yet are especially harmful to those less generously endowed. The various diseases of the genitalia are adequately described in text books and the influences on fertility are well known. The biopsies of testicular tissue have revealed, in some instances, marked thickening of the fibrous tissue encircling the seminiferous tubules. An explanation for this is not ventured herewith, but it is conceivable that these deposits may act as barriers and prevent proper nourishment of the germinal epithelium. This affords a probable example of a non-refractory end organ incapable of being stimulated.

No claim is made that the examination of the biopsied testicular tissue will depict which one of these foregoing conditions has caused aspermatogenesis. The inconsistent results of treatment are more fully appreciated, for response depends on: the identification of the cause, the use of appropriate corrective agents, and the ability of the testes to respond to such stimulation. Testicular biopsies will not solve all these problems, but will obviate some of the difficulties. The information gained from the biopsy will certainly prevent some men from re-

ceiving innumerable injections of hormones when the testes are proven to harbor large numbers of spermatozoa, or are atrophic to a hopeless degree. A selection of favorable cases for treatment is made possible and a reasonable trial is given to substances purported to have therapeutic value.

Occlusions in the seminal passageways, as well as faulty spermatogenesis, may cause absolute sterility in men. The majority of acquired obstructions are located in the lower portions of the epididymes or beginning of the vasa. Two cases of congenital absence of the vasa have come under my care during the past two years. Notwithstanding the fact that a normal outlet for spermatozoa had never been available, the testicular biopsies demonstrated fairly normal spermatogenesis. The ability of the testicles to maintain their function despite years of obstruction is in harmony with the theories that the epididymes are capable of absorbing and disposing of spermatozoa. These organs, rather than the seminal vesicles, are perhaps the true "graveyards of the spermatozoa." This cyclic process of production and absorption may account for the entire absence of sperm in the semen even though a few mature sperm are seen in some biopsies showing faulty and poor spermatogenesis.

Clear indication for operation is afforded by the aid of biopsies. An obstruction or congenital anomaly of the efferent tract is to be inferred if several ejaculates have no sperm yet the biopsy shows well-differentiated germinal epithelium with many mature spermatozoa.

A second operation is then performed and a full exposure of the scrotal contents is obtained. The patency of the vas is tested by injecting a fluid into its lumen at a level with the body of the epididymis. The epididymis is punctured at a corresponding point and the expressed secretions are examined immediately for sperm. If the vas is patent and sperm are found a union of the two structures is formed after the method which Martin described forty years ago. Arterial silk sutures serve as excellent material for the juncture of vaso-epididymal anastomosis. If patency is established, sperm will appear in the ejaculate within 12 months. Failures are due to inability to complete the operation because of extensive obstructions along the vas, or subsequent postoperative closure of the fenestra between the vas and epididymis. The operation may also fail to bring clinical results for, although at least one tract has been opened, too few or immotile sperm are ultimately secured in the semen. Successful results should reach about 20 per cent of those operated

upon, and yet the failures are no worse off than prior to operation. In retrospect, it may be said that all too often such men are dismissed as hopeless and that, if they are willing to accept unfavorable odds, the operation deserves trial.

SUMMARY

External examination of the male genitalia does not always indicate the state of spermatogenesis or condition of the epididymes and vasa. Testicular biopsy is a practical method of appraising the value of the spermatic tissue. Appropriate treatment can be applied and useless therapy avoided. The inconsistent results of treatment of grave disorders of the germinal epithelium are commensurate with the existing etiological and therapeutic problems, but future research promises much for the development of efficient treatment.*

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* Six case histories with microphotographs, illustrating the usefulness of testicular biopsies, were included in the original presentation of this paper.

THE EPIDEMIC CONSTITUTION IN HISTORIC PERSPECTIVE *

IAGO GALDSTON

SCIENTIFIC epidemiology . . . began like almost everything which makes life worth living, in Ancient Greece." (Major Greenwood) In the books of Hippocrates entitled *Airs-Waters-Places*, and *Epidemics I-III*, we have the beginnings of epidemiology. The first is an essay, which exhorts the physician to appreciate the influence of environment, season, and mode of life, on health and disease. The second, *Epidemics I-III*, offers, in a sense, case notes to illustrate the propositions expounded in *Airs-Waters-Places*.

There are critics who find fault with these books, for in them, intermingled with the astute epidemiological observations, are to be found comments on critical days, on coctions, crisis, and crasis, and these they find repugnant. But such critics are rather superficial for in their objections to particular details they lose sight of the basic thought. That which entitles Hippocrates to be considered the founder of scientific epidemiology is not his speculations on the origin of the Scythians' impotence, nor his theory on the critical days, but is rather an understanding vast and profound. That understanding is of man's relationship to his universe both immediate and remote. This appreciation is leavened in all the genuine works of Hippocrates. It is the compelling warrant for his rejection of the supernatural or deistic origin of disease. It illuminates and rationalizes his therapeutic practices. It holds within the bounds of sense and reason his diagnoses, his prognosis, and his nosography. It accounts for his dependence on nature to effect the cure. But his deeply philosophical appreciation of man's relationship, and of man's susceptibility in health and disease to the interplay of the forces in his environment is best revealed in Hippocrates' epidemiological books. These books, as Jones observes, are without pretensions to literary form, but they constitute "the most remarkable product of Greek science" (W. H. S. Jones, *Hippocrates*, Vol. I, p. 141). Their

* Delivered December 31, 1941 before the History of Science Society Meeting, in association with The American Historical Association, Chicago, Illinois.

distinction lies less in what is expressed than in what is implied in their texts. These books are the products of maturity, the yield extracted by time and much meditation from a vast and varied experience. In these works Hippocrates advances the simple thought that man's private ills are chiefly the result of his own ignorance and of his slovenliness, but the epidemic diseases are the resultant of inimical forces, of disequilibria in man's environment. In *Airs-Waters-Places* Hippocrates expresses the dictum that he who wishes to pursue properly the science of medicine must consider the effects of seasons, winds, the properties of waters, those of the soil, and "the mode of life also of the inhabitants that is pleasing to them, whether they are heavy drinkers, taking lunch, and inactive, or athletic, industrious, eating much and drinking little." (W. H. S. Jones, *Hippocrates*, Vol. I, p. 71-72). There is revealed in this short passage a wealth of insight, the penetrating appreciation of man's position in the intricate web of Nature.

It is an easy yet pardonable fault to read into the writings of Hippocrates more than he ever knew or intended, and to credit him with wisdom and knowledge born in later years. Our evaluation of the Hippocratic writings on epidemic diseases, however, is free of these faults. It were difficult rather to prize them excessively, for they are unique and stand alone for many ages. There is nothing in what has come down to us from the ancient medical writings that even remotely suggests that in these matters there had been a forerunner to Hippocrates.

Nothing in the speculations of the contemporary philosophers corresponds to the basic idea propounded in the Hippocratic writings on epidemiology.* On the contrary, Hippocrates, in the book *Nature of Man*, shows scant respect for the theories and speculations of the philosophers.

Hippocrates was a naturalist who in the mosaic of life counted man as a creature bound with all the rest in the common matrix of earthly forces. Four hundred years later the Latin poet Lucretius (95-52 B.C.) eloquently, though somewhat mordantly, espoused a similar naturalism.

In *Epidemics*, which I have characterized as case history illustrations of the thesis of *Airs-Waters-Places*, we come upon the Greek term *καταστασις* derived from *καταστημα* and defined (Liddell & Scott) as "a state, situation, condition, constitution, quality."

* See in this connection: Friedrich, Carl, *Hippokratische Untersuchungen*, Berlin, Weidmannsche Buchhandlung, 1899, p. 130, p. 162.

In the authoritative translations of Hippocrates *katastasis* is rendered as "constitution." It is well for us to note this term, for about it revolves much of later epidemiological thought—and I may add, confusion. In the Hippocratic works *katastasis* connotes environmental factors contributing to the engenderment of epidemic diseases. In later times, the term *katastasis* was sheared of its Hippocratic meanings, and while commonly employed, was assigned a variety of meanings. We will return to the *katastasis*, or more specifically to the epidemic constitution, later. To sustain the thread of our story we need to trace further the history of epidemiological thought. But trace is hardly the fitting word; we rather march with seven league boots over a stretch of some thirteen hundred years.

The revival of epidemiology is to be credited to the French physician Gulielmus Ballonius, and to Thomas Sydenham. Ballonius was the earlier of the two. He was born in Paris in 1538 and died in 1616, having attained to the age of seventy-eight. Sydenham was born eight years after the death of Ballonius, that is in 1624. Ballonius carried on in the best Hippocratic tradition—to observe, to report, to reflect. In his *Epidemiorum et Ephemeridum*, published after his death by his nephew, in 1640, Ballonius follows the pattern of Hippocrates. He gives the *katastasis* of the years, and then reports the cases he had seen. We have in these works a catalogue of clinical records. But we have here little else. Ballonius follows the pattern but adds nothing to the knowledge proffered by Hippocrates. It is quite otherwise with Sydenham. He too returned to Hippocrates, but he went further than Ballonius in the pursuit of the problems of epidemiology. His epidemiological writings offer us no clinical case records, such as those of Ballonius afford, but they do tease the heart of the matter, the epidemic *katastasis*—or, in Sydenham's words, the epidemic constitution.

It is not possible in this discursive review of the history of epidemiology to expound minutely, to so-to-say comb, spin and reweave the fabric of Sydenham's thoughts on epidemiology. Moreover, that has been done exceedingly well by Major Greenwood. I will rather borrow and adopt Greenwood's lucid summation of Sydenham's epidemic constitution.

"The complete morbid process of an epidemic disease is made up of two parts; the first is specific (the a, b, c, &c., of the formula), subject to secular modification and also to short period oscillations—

i.e., it is a doubly periodic function of the time. The second part is generic, common to all species of epidemic diseases and a function of some terrestrial conditions included under the term "Epidemic Constitution."^{*}

It is this second part, the generic component of the epidemic constitution, defined not exclusively in terms of atmospheric conditions but rather as "a function of some terrestrial conditions" which constitutes Sydenham's most valuable contribution to epidemiological thought.

Sydenham's works on epidemiology gave impetus to the study of the subject but what followed was not in the order of the original. The later works are lacking in philosophical insight, in breadth of understanding. They are provincial rather than catholic. They are painstaking, and scrupulous collections of meteorological data. They are inspired by the vain hope that the secret of epidemic diseases could be wrested from the collected data on barometric pressures, temperatures, humidities, wind directions and velocities, and rainfall. In the two volume edition of Sydenham's collected works published by the Brothers de Tournes in Geneva, 1736, there are included twenty-one contributions on epidemiology from the pens of twenty authors. Among them we find the illustrious Ramazzini. These contributions are uniformly devoted to reports on climatic conditions prevailing in given localities during given periods of time, and to notations on the diseases current during those periods and in those locations.

To catalogue the different authors who attributed epidemic diseases to the depraved constitutions of the atmosphere, listing their individual and differing opinions on the source of the atmospheric corruption were a large and profitless task. It is more profitable to abstract from this enormous mass of published opinion, theory, and notation, its common factors, for we can thus identify the *vis a tergo* that motivated and directed the thinking and labors of these men. To achieve this we must rise above the particulars to survey the broad terrain.

It is patent that the time span of two thousand years, covered thus far in our review, embraces three epochs in thought on epidemic diseases. These we may designate as the epochs of Hippocrates, of Sydenham, and of the climatological epidemiology.

^{*} Major Greenwood: Sydenham as an epidemiologist, *Proc. Roy. Soc. Med.*, London, 1919, Epidem. Sect., vol. XII, Part II.

We have dealt at length with the Hippocratic epoch, but less amply with the other two. To appreciate what with some broad license I term the phenomenon of Sydenham, we need to grasp clearly the temper and spirit of his age. During Sydenham's lifetime the medical renaissance initiated by Thomas Linacre (1460-1524), the "restorer of learning" in England and first president of The Royal College of Physicians, reached its culmination. Sydenham was the last of the great English physicians who were nurtured in the ancient medical lore which the classical renaissance had resurrected and revived.

Sydenham lived in the age of Shakespeare, Bacon, Milton and Dryden, of Galileo, Kepler, Descartes, Boyle and Newton, and of William Gilbert of Colchester, William Harvey of Folkestone, and John Locke of Wrington. But Sydenham did not fall under the even sway of all these greatest among English poets, philosophers and scientists. Thus, it does not appear that either Harvey, or Boyle, or Descartes, or Newton moulded his thinking. Sydenham was indeed, as his followers fittingly described him, the English Hippocrates. With Sydenham the Renaissance came to an end and the dawn of a new age was ushered in, the age of modern science, with its instruments of precision, and its inductive techniques.*

Thought was now on a new tangent. Man found anew his own "bright earth" and, himself. With consuming eagerness he set out to explore the microcosm. With the aid of his balances, his microscopes, his thermometers and barometers, his measuring rods and his chemical reagents he uncovered the wonders of the universe. A new enchantment was upon him, one that alienated him from his former devotions. It is this new enchantment, the limitless faith in inductive science, that accounts for so many men's eager scrutiny of the atmospheres for the secret of the epidemic diseases and for the conviction shared also by numerous others, that the noxious principle could be isolated from the complex of man's physico-chemical environment.

The *katastasis* of Hippocrates was for the while forgotten. But the study of epidemics continued, nay was pursued with even greater intensity. This study developed along three tangents: statistical, historical and bacteriological.

The statistical study was initiated by John Graunt, the son of a

* Within the lifetime of Sydenham, Harvey published *De Motu Cordis*, Descartes his *Méthode*; Boyle performed his revolutionary physico-mechanical experiments; Malpighi initiated his histological studies; Leuwenhoek discovered the protozoa; Hooke published his *Micrographia*, John Graunt drew up his *Bills of Mortality*, and Newton issued his *Principia*.

London draper, who himself became a prosperous shopkeeper and a Fellow of the Royal Society. In 1662 Graunt published a volume of statistical deductions based on the Bills of Mortality. He thus opened a new terrain which yielded to his followers most illuminating data on the dynamics not only of epidemic diseases but of a vast variety of other social and biological phenomena.

The history of epidemic diseases was, of course, of continuous interest to man, and was even intertwined in his chronicles with the tales of the fortunes of men and of states. Toward the end of the Eighteenth Century, however, the history of epidemic diseases was cultivated as a special discipline. The names of Philipp Gabriel Hensler, Leonhard L. Finke, Noah Webster, J. A. F. Ozanam, August Hirsch, J. F. C. Hecker, and Charles Creighton are preëminent in the history of epidemic diseases. Creighton's *A History of Epidemics in Britain* is without doubt the "capo lavoro" in this field. It is rich in scholarship, profound in understanding and enormously wealthy in factual data.

Before the influenza pandemic of 1918 swept the earth, most of the historical data on epidemics that had been gathered in the preceding centuries, was considered by most epidemiologists and physicians to be only so much curious lore by which to witness the blind gropings of the pre-bacteriological eras. However, the devastating influenza plague of 1917-1918 which dwarfed in its destructiveness the ravages of the World War, jolted at least a few among the epidemiologists out of their smug and patronizing state of mind. These epidemiologists rediscovered the precious worth of the historical studies on epidemics, and they have since made splendid use of the facts and ideas which these studies afford. The use that is lately made of the historical data will be dealt with later.

There remains to be mentioned the last of the three tangents of epidemiological development pursued since the days of Sydenham, namely, the bacteriological. The history of this development is too well and too commonly known to require elaboration. It need only be recalled that with the discovery of the disease-producing bacteria, epidemiology promptly became identified with bacteriology, so that the two were almost considered synonymous terms. Pettenkofer's was the last brave stand of the "constitutionalists" against the bacteriologists. Thereafter bacteriology held undisputed mastery over epidemiology. There were of course rebels, and heretics; but they were as voices in

the wilderness. Major Greenwood neatly sums up the situation in the following words:

"It is true that some of the leaders of the victorious bacteriological army, including Koch himself, warned us that the discovery of parasites and the elucidation of their life histories left much of the mechanism of herd illness unexplained, but some of the commissioned officers and all the camp followers of the army would know nothing of this caution. It came to be believed, is still believed by a majority, that epidemiology, from the scientific point of view, is a mere appendix of bacteriology, that when the means of infection and the vehicles of infection have been identified, the problem of an outbreak of herd sickness is solved. All the ideas of the ancients were dismissed as archaeological lumber and the work of such writers as Farr, Brownlee, and Ross politely ignored, taken to be mathematical, and therefore intellectually respectable, but of no practical importance."*

Such was the state of epidemiology during the first decades of the present century. Such it is this very day for most medical men. Two departments share between them the whole terrain of epidemiology: one is the statistical department; the other, the bacteriological. During the last two decades, however, there has developed in the field of epidemiology a revival of interest in that which has for so long been forgotten and neglected—the *katastasis* of Hippocrates, the epidemic constitution of Sydenham—and this has come about in the most interesting and diverse of ways.

The precipitating cause of this revival was the last great influenza pandemic, but antecedent to it there were prodromal signs of disaffection to be noted among a small body of epidemiologists; disaffection with the neat and final assumption that the discovery of the *materies morbi* and of the methods and agents of their transmission resolved all the problems of epidemiology. The influenza pandemic inspired these dissidents with greater courage. Crookshank (F. G.), Greenwood (M.), Goodall (E. W.), and Hamer (Sir W. H.)** are the names outstanding among those who since 1918 "aroused greatly increased interest in

* *Epidemiology Historical and Experimental* by Major Greenwood (Herter Lectures for 1931—Johns Hopkins Press, Baltimore, 1932).

** F. G. Crookshank: Chadwick Lectures, 1918. (Abst.): *Med. Press & Circ.*, 1918 clvii, 291; 310; 329—M. Greenwood: Sydenham as an epidemiologist, *Proc. Roy. Soc. Med.*, 1918-19, xii, *Epidem. Sect.*, 55, 61—E. W. Goodall: The epidemic constitution, *Proc. Roy. Soc. Med.*, 1927-28, xxi, *Epidem. Sect.*, I.

the study of epidemics from the natural history point of view, and tended to discourage meek acceptance by epidemiologists of a belief that all that was required of them was to rewrite epidemiology in terms of causal organisms.”*

In 1925 F. G. Crookshank spoke up in fine sarcasm:

“Whilst leaving the bacteriologists to pursue their researches to a successful issue in the seclusion of their own laboratories—for it were impious to believe that persons who ignore clinical and epidemiological data are not the predestined solvers of clinical and epidemiological problems—it may be profitable to discuss briefly two questions that, although nowadays regarded—at any rate in the best medical circles—as hardly worthy of scientific investigation, have nevertheless engaged attention since the earliest ages. These questions are, first, that of the periodicity of the recurrent pestilence we now call influenza, and, secondly, that of the dependence of these recurrences upon, or their correlation with, what used to be called telluric and cosmic influences.”**

The exploration of these two problems, the periodicity of recurrent pestilences, and their dependence or correlation with “what used to be called telluric and cosmic influences” now yields astonishing and illuminating information; astonishing because unanticipated; illuminating because it conforms with our best knowledge in medicine.

In the effort to trace the periodicity of recurrent pestilence one comes upon the realization that history presents a spectacle which can be properly described as “a succession of new plagues for old.” This realization invalidates old beliefs, for it has been common to think of historical time in relation to epidemics as divisible into two portions: one enormously long, and the other comparatively short. The segmental line which separates these time portions corresponds to the period of the discovery of the pathogenic microorganisms. Thus the antecedent, earlier, greater stretch of time is characterized as that period during which the epidemic diseases ravaged a helpless mankind, while the later period is labeled the age in which mankind by means of modern science, and most notably through all that goes under the name of bacteriology and immunology, mastered, one, by one, the plagues of antiquity. This characterization of time-experience is misleading and

* Sir William Hamer: *Epidemiology Old and New*, London, Kegan Paul, 1928.

** F. G. Crookshank: *Epidemiological Essays*, London, Kegan Paul, 1930.

erroneous. History, to repeat, presents rather a continuous pageant of plagues, the unbroken succession of new plagues for old.

The plagues of antiquity cannot be lumped together. True, some among them, for instance bubonic plague and influenza, are as old as mankind. But others are distinctly of later origin, and some are very modern indeed. Bearing in mind that we are considering diseases in epidemic form, and *not* diseases as nosographic entities, we cannot help but recognize some herd diseases to be what the Germans call "Zivilisationsseuche," plagues of modern civilization. Among such we can list tuberculosis, cholera, typhoid, diphtheria, scarlet fever, and cholera infantum. This is not a complete list, and to it should perhaps be added certain of the psychological disorders, notably schizophrenia. But it is long enough a list to illustrate our thesis. Among the ancient epidemic diseases, those prevalent before the Christian era, we can list bubonic plague, malaria, and typhus, while during the medieval ages we can count smallpox, leprosy, syphilis, and influenza. It is pertinent to bear in mind that all of these disease entities very probably, and most likely existed since the most ancient days. None of them is assumed to have come into being within historical time. Only as *epidemic diseases* are some certain ones labeled new, or recent. Hence it is a provocative and pertinent problem that confronts us, this problem of the succession of plagues, the demarche of new plagues for old. And, where else can we hopefully look for the solution of this problem but among "what used to be called telluric and cosmic influences." Granting that the "contagium vivum" was ever present, as appears to have been certainly the case with the tubercle bacillus, why was it, for example, that tuberculosis did not achieve the magnitude of a great epidemic disease until the Eighteenth Century? * Why was not Europe plagued by cholera, or diphtheria, or typhoid until what we call modern civilization became well advanced?

There are some, of course, who deny the validity of these questions; who maintain that Europe was indeed plagued by these diseases, but that physicians lacking diagnostic and clinical acumen did not recognize them. Such a protest is but conceit articulate, the arrogance of an ignorance that scorns the past. To this protest the gentle words of Richard Mead form a fitting retort.

"For it must be believed that the first masters of our art who

* Quotation from Brownlee.

are so careful in describing and distinguishing the signs of all diseases would not have briefly mentioned them but would have described them at length if they had but known of these at once terrible and contagious diseases.”*

There can be no doubt that some epidemic diseases have been, and are, new sprung in the succession of time. And their origin is rooted in telluric and cosmic influences. Does this last statement sound like a profession of faith in astrology? Then it misleads. But who can gainsay the splendid findings of modern climatology, the painstaking work of Elsworth Huntington and of C. A. Mills, which reveal most definitely the bearing of climate upon the prevalence of disease. By telluric and cosmic influences we however intend more than climate, more than even airs, waters, and places. We intend all that was embraced by the Hippocratic *katastasis*: The entire physical environment of the people and in addition their cultural, industrial, and economic status.

I offer a brief and somewhat tentative illustration as to how changes in telluric and cosmic influences can contribute to our understanding of the historical succession of plagues. Let us review the experiences of the European peoples, notably the English, during the last three hundred years and see what bearing they may have on the new plagues which these people experienced. The period under consideration corresponds to the development of the modern industrial system. This as we know embraces the substitution of the machine for hand tools, the growth of the factory and of the modern industrial community, and the creation of a new social class, the proletariat, the class that has but one commodity to sell, its labor power. Such in brief is the common summation of the technological, economic changes experienced during the industrial revolution. But there transpired during this period certain other changes, of “telluric and cosmic” character; changes which affected large masses of people. The import of these changes, particularly in relation to epidemiology, is little appreciated. In the industrial revolution humanity experienced an unparalleled dislocation in its environmental relationships. Never before in its history was there such population density, such prolonged and close compaction of persons in factories and slums. The industrial revolution removed large masses of people from the soil, distanced them from their food sources, changed

* Quoted by Rolleston, J. D.: *The History of The Acute Exanthemata*. (The Fitzpatrick Lectures for 1935-36) London, Wm. Heinemann Ltd., 1937.

their diets, altered their foods, bound them by an exacting discipline never before experienced. The industrial revolution broke up the rural community, disrupted the homestead, dismembered the family. For millions of human beings "airs, waters, and places" were changed, for the worse. The whole social and ethical realm was altered. Old values lost their validity, old relationships, their force and strengths. In the light of all this can we doubt but that these "telluric and cosmic influences" engendered an "epidemic constitution," which favored the rise of the "*Zivilisationsseuche*"? And, what is perhaps more significant, in that it bears on our present day medical problems, can we doubt but that in order to overcome these plagues, the *epidemic constitution* must be altered? It is interesting to observe for how long this was a belief shared by the more profound students of epidemiology, albeit the others did not know or understand it. Sydenham groped about it, but never seemed to grasp it clearly, though Greenwood believes he did. In his essay on *Sydenham as an Epidemiologist* Greenwood states:

"The bacteriologist—or, at least, his popular exponent—holds that all diseases can be attacked and conquered seriatim by specific measures; isolate the organism, "stamp it out" or procure an artificial immunity and that disease is "conquered." But if my interpretation of Sydenham's constitutions is correct, all that can be achieved in this way is either to reduce the number of stocks upon which a stationary fever may be grafted or to reduce the number of stationary fevers, leaving the stocks upon which the remainder may be grafted untouched. *Naturam expellas furca, tamen usque recurret*, hence Watt's theory of substitution, and Sydenham's constitutions. So the problem of preventive medicine becomes wider and we are led to ask whether what is wrong with the unhealthy may not be not infection with this or that germ but—unhealthiness, even as the chief trouble of the poor is not addiction to public houses but just plain poverty."*

William Farr also had a faint appreciation of the dominant significance of the epidemic constitution, for in his Thirtieth Annual Report he wrote:

"It is, however, by no means proved that the general mortality under unfavourable sanitary conditions is much reduced by render-

* M. Greenwood: *Sydenham as an epidemiologist*, *Proc. Roy. Soc. Med.*, Sect. of Epidem., London, 1919, vol. xii, parts i & ii.

ing a child insusceptible of one type, while he remains exposed to all other types of zymotic disease.”*

Dr. Ozanam writing in 1817 differentiated clearly between the epidemic proper and the epidemic constitution. He defined the epidemic constitution as “an indeterminate period during which diseases occur, which though they seem to have different characteristics; nevertheless, have the same origin and the same diathesis. It is an unique disorder of which the various forms are, so to say, only symptoms and which requires only one general method of treatment.”**

Again Ozanam states:

“The epidemic constitution has a more general influence upon the human being, but its effect is felt only in an irregular and diversified manner producing a variety of diseases; whereas the effect of the real epidemic is more direct, more uniform and more marked and neither hidden nor disguised as that of the former.”***

All of these authors, and others beside, sensed the significance of the epidemic constitution, and defined its nature with varying degrees of acuteness. Most of them conceived of the epidemic constitution in the narrower meaning of telluric and cosmic influences, in terms principally of climatological and terrestrial factors. They knew there was more than these elements in the epidemic constitution, but they did not know the nature of the unknown “more.” They could not even conceive of them. They, as all medical men, then thought of noxious states as due to the presence and operation of inimical agents or forces. They could not conceive of morbidity arising from the *absence* of subtle and essential factors. But then this realization, this recognition of disease resulting from a minus rather than from a plus state is the most recent achievement of medical science.

It is rooted in the epoch marking discoveries in the realms of endocrinology and of nutrition. This matter commands our attention, for in it lies much of the account for the vain gropings of the epidemiolo-

* Quoted by M. Greenwood: *Epidemics and Crowd-Diseases*. London, William & Norgate Ltd., 1935.

** “Une constitution épidémique est un espace de temps indéterminé durant lequel règnent des maladies qui, quoique d'un caractère différent en apparence, n'en ont pas moins toutes la même origine et la même diathèse. C'est une maladie unique, dont les formes variées ne sont, pour ainsi dire, que des symptômes, et qui n'exige qu'une seule méthode générale de traitement.” J.A.F. Ozanam: *Histoire médicale générale et particulière des maladies épidémiques, contagieuses et épi-zootiques*. Paris, Lyon, 1817, p. 40.

*** “La constitution épidémique a une influence plus générale sur l'espèce humaine; mais son action ne se fait sentir que d'une manière irrégulière et diversifiée, ce qui produit la variété des maladies qui en dérivent; au lieu que l'épidémie a la sienne plus directe, plus uniforme et plus marquée sur les individus qu'elle attaque, et cette action n'est point latente ou masquée comme dans la première.” J.A.F. Ozanam: *Histoire médicale générale et particulière des maladies épidémiques, contagieuses et épi-zootiques*. Paris, Lyon, 1817, p. 42.

gists of the preceding centuries for the unknown factors of the epidemic constitution. They searched man's realm for a something that was not there, in a manner that could not reveal it. They sought for a positive entity. They contemplated biological man as the stationary passive fixed entity upon whom the forces of the universe play their mysterious will. This viewpoint can be witnessed in two remotely diverse authors. Ludwig Edelstein in a most interesting philological analysis of the Hippocratic book *ΠΕΡΙ ΑΕΡΩΝ* is distressed by Hippocrates' preoccupations with the healthy man. Edelstein contends that "To be healthy means: not to be ill," the life of the healthy, he believes, does not concern the physician. The Greek physician's conviction that health has no being but is rather a perpetual development, he labels as something strange to modern people. The whole of this brilliant study, I might add, misconceives the substance and intent of the book *Airs-Waters-Places*. But Edelstein only shares in the reigning beliefs that disease is the positive state, that it is the resultant of aggressive forces which assault man's constitution, that health is only the absence of disease.

Von Behring is the other author whom we may call in witness. In the introduction to his *Gesammelte Abhandlungen zur ätiologischen Therapie von ansteckenden Krankheiten*, von Behring states his credo in the following words:

"... For we are of the opinion that in combating diseases we can achieve more by attacking the causes of disease than by an attack on the living cells and organs."

"Until now we only know that even the best intended, direct attacks on living cells and organs in order to animate or to stimulate them into a state of modified activity, are more likely to harm the cells and organs, than to bestow upon them more health and resistance."*

We know today that it is eminently possible to influence the living cell. We know that to a very great extent the competence of the specific disease-producing agents to injure the living body depends upon the telluric and cosmic influences which antecedently affected the living body. These influences are collectively embraced in the epidemic constitution.

By all these considerations, and by their implications, suggested but

* E. Behring: *Gesammelte Abhandlungen zur ätiologischen Therapie von ansteckenden Krankheiten*. Leipzig, Georg Thieme, 1893, p. LXX, LXXI.

not elaborated in this presentation, we are compelled to conclude that what Hippocrates intended by *katastasis* is the more important factor in epidemic diseases, that modern medical advances have validated his contentions, and have elaborated on the components of the epidemic constitution.

Finally we sum up the results of our study in this dictum. To the extent that medicine fails directly and indirectly to ameliorate the inter-relationships of man and his life's realm, it can succeed only in deferring mortality but not in decreasing morbidity, and it may be taken as a corollary that to the extent that mortality is deferred, and life prolonged, to that extent is morbidity multiplied and increased.

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ILL, EDWARD JOSEPH: 1004 Broad Street, Newark, New Jersey; born in Newark, May 23, 1854; died in Island Heights, New Jersey, June 9, 1942; graduated in medicine from the College of Physicians and Surgeons, Columbia University in 1875; elected a Fellow of the Academy February 1, 1894.

Dr. Ill was formerly surgeon to Woman's Hospital and medical director of St. Michael's Hospital; gynecologist, supervising obstetrician and trustee of St. Barnabas Hospital; consulting gynecologist, Beth Israel Hospital, Newark, All Soul's Hospital, Morristown, Mountainside Hospital, Montclair, and the Rahway Memorial Hospital, Rahway. He was a Fellow and member of the Board of Governors of the American

College of Surgeons, a Fellow of the American Medical Association, past president of the Essex County Medical Society and the Medical Society of the State of New Jersey; a diplomate of the American Board of Obstetrics and Gynecology; in 1893 vice-president, in 1899 president, and member of the executive council from 1901 to 1903 of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons; vice-president for New Jersey of the Pan American Medical Congress in 1893; member of the Southern Surgical Association, chairman for the State of New Jersey of the American Society for the Control of Cancer; a member of the Board of Education of Newark from 1878 to 1880; for many years state director of the Prudential Life Insurance Company of America; and a member of the American Radium Society, the American Association for Cancer Research, the Southern Surgical Society, the New Jersey Surgical Society and the Academy of Medicine of Northern New Jersey.

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED
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OCTOBER, 1942

ADJUSTMENTS OF NERVE ENDINGS*

CARL CASKEY SPEIDEL

Professor of Anatomy, University of Virginia

Harvey Lecture, January 16, 1941

THE nerve cell is the structural unit which underlies nervous activity. Nerve cells function in groups and in chains, the separate cells being linked with one another at synapses through their nerve fiber endings. Nerve endings are also the structures which receive impulses from the sensory apparatus and deliver impulses to the motor apparatus. It is obvious, therefore, that changes and adjustments in nerve endings may be of profound importance.

In his classic work Cajal¹ has presented a very complete picture of microscopic changes in nerve cells and endings as these undergo degeneration and regeneration in various parts of the peripheral and central nervous system. His observations were made on fixed and stained material. Such a technique did not permit observations of the sequence of changes in the same individual endings. Nevertheless, Cajal had no difficulty in recognizing the normal resting nerve ending, the ending with a growth cone at the tip, and the retracting ending with a retrac-

* This work has been aided by grants from the Grants-in-Aid Committee of the National Research Council, the Committee on Research of the American Philosophical Society (from the Penrose Fund), and the Committee on Scientific Research of the American Medical Association.

tion club at the tip. He also recognized that nervous autotomy sometimes occurred.

After his invention of the tissue culture method Harrison² made the first important direct observations on the living young nerve fibers as these grew out from explanted nerve cells. He described in detail the activities of the growth cones and the part they play in the spinning of new nerve fibers. Many other investigators have since used the tissue culture method in studying nerve cells explanted from various parts of the nervous system.

An interesting and significant point is that so far in tissue culture the myelin sheath has not been differentiated. This is true even in cultures in which nerve cells and neurilemma cells are kept in intimate association with one another. The nerve endings that are present in tissue cultures, therefore, can hardly be regarded as mature endings of the type that in the living animal represent the terminations of myelinated fibers.

Some years ago I found that it was possible to watch individual nerve fibers for prolonged periods in living frog tadpoles. A simple technique was used involving microscopic examination of the animal in a special upright chamber, the animal being temporarily immobilized with a weak anesthetic. With care the entire history of the same nerve fiber could be obtained for periods of several days or weeks, the animal being kept in good condition throughout the observations. Moreover, it was found possible to take satisfactory ciné-photomicrographs revealing minute details of the changes in nerve fibers and their endings. Especially valuable were pictures of the "fast motion" type which vividly revealed relatively slow changes.

The growth of individual nerve sprouts, the movements of neurilemma cells, and the process of myelin sheath formation were first studied.^{3,a,b,c} This was followed by experimental studies of the phenomena accompanying nerve irritation and recovery, injury and repair,^{3,d} and by studies of the effects on nerve fibers of alcoholic intoxication^{3,e} and metrazol treatment.^{3,f} Recent work, not yet published, has dealt with the effects on nerve fibers and their endings of electric shocks and of insulin treatments. The increasing use of shock therapy in the treatment of human mental disorders makes this field of investigation of timely interest. Other recent work, also as yet unpublished, has dealt with the changes in nerve endings during periods of normal rapid growth in size of the animal, during alternating periods of starvation

and good nutrition, during alternating periods of exposure to strong and weak anesthetics, and during temperature variations.

In this lecture I propose to give an account of the fundamental structural changes in nerve endings that are discernible under both normal and experimental conditions. This account includes changes associated with growth, regeneration, starvation, treatments with chloretone, alcohol, metrazol, insulin, electricity, hypertonic salt solutions, X-rays, and temperature variations. This account also includes adjustments of nerve endings associated with local tissue changes, such as occur during the progress of myelination, during tissue regulation after wound infliction, during the establishment of collateral innervation after experimental denervation of nearby territory, and during various local cellular movements.

OBSERVATIONS AND EXPERIMENTS

A typical mature tree of endings of a myelinated fiber is shown in the accompanying illustration (Fig. 1).^{*} This sketch gives the appearance not only of the ordinary endings in the resting stage but also of those in stages of growth, retraction, irritation, and degeneration.

EXTENSION AND RETRACTION OF NERVE ENDINGS DURING EARLY GROWTH AND REGENERATION

The phenomena of marked extension and retraction are most readily to be seen at the tips of young or rapidly regenerating nerve fibers. In the living frog tadpole at an early stage of development cutaneous nerve fibers may be watched as they grow out toward the skin (Fig. 2). Typical mobile growth cones are present at the tips. These advance in somewhat sporadic fashion. The rate of progression, therefore, is subject to great variation. About 40 micra per hour represents rather rapid growth. At the tips of the proximal stumps of regenerating nerve fibers growth cones also develop and move out in similar fashion.

Second and later growth cones of other nerve fibers follow the line laid down by the first and a small nerve is thus formed. The fibers are naked at first. Soon, however, neurilemma cells move out along the nerve, multiply, and play an important role in the formation of both myelin sheath and neurilemma. Characteristic terminal arborizations, such as are shown in Fig. 1, ultimately develop on myelinated fibers,

^{*} All figures except the last (Fig. 18) represent nerve fibers in the tail of the frog tadpole.

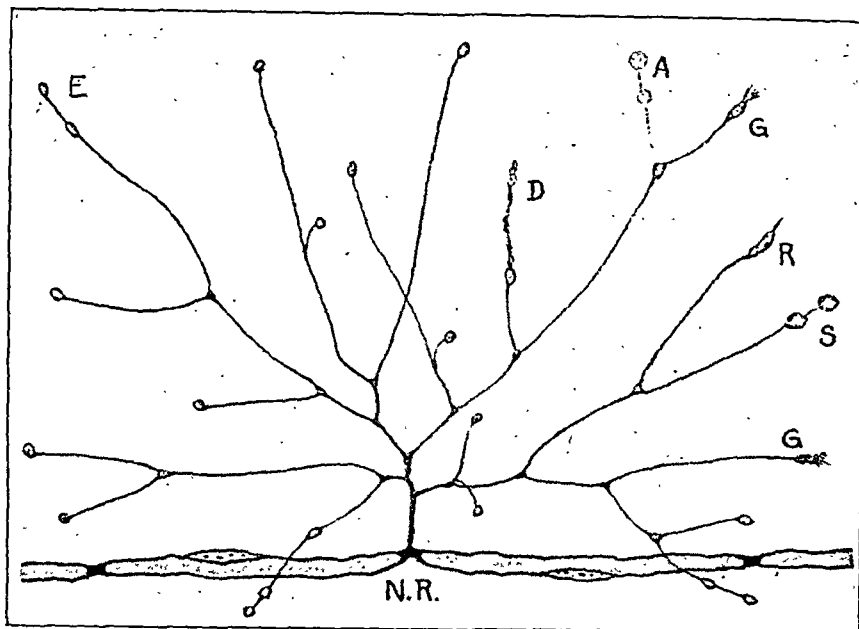


Fig. 1—Diagram showing a cluster of cutaneous nerve endings. At a node of Ranvier (N.R.) a collateral branch is given off which subdivides as shown. At the tips of most of the branches are typical resting endings (E). Two endings are characterized by growth cones (G), one by a retraction club (R), and one by a markedly swollen condition (S). A short length of one branch is in degeneration (D) and another in process of autotomy (A). This illustration of frog tadpole nerve endings peripherally located affords an interesting comparison with that of cat nerve endings centrally located (cf. Fig. 18).

not only at the end of the most distal myelin segment, but also at collateral side branches which appear at some of the nodes of Ranvier. At the tip of each branch of a terminal arborization is a small spherical or ovoid end bulb (bouton). Any one of these, however, may become transformed into a growth cone and advance, or into a retraction club and retreat.

Rapidly growing nerve endings under certain conditions may cease their advance and then undergo rapid retraction. This sometimes takes place spontaneously. It may also be induced readily by various experimental procedures. Among the methods which I have used to bring about retraction of growth cones are the following: treatment with alcohol, chloretone, metrazol, insulin, electricity, heat, hypertonic sodium chloride solution, starvation, and wound infliction by cutting or bruising nearby tissues with resulting general tissue adjustments.

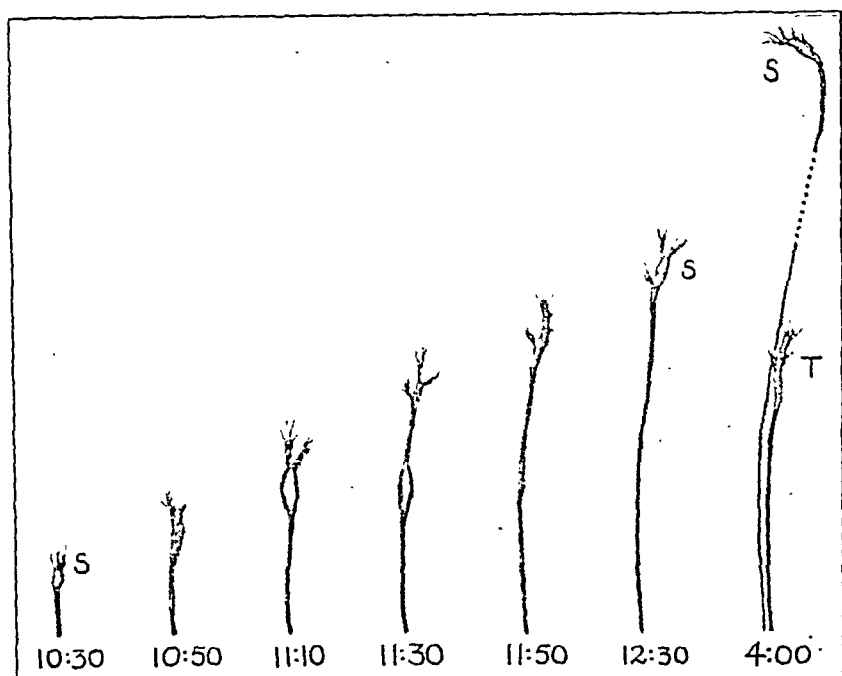


Fig. 2—Normal rapidly growing nerve endings in a young tadpole shortly after hatching. A pioneer growth cone (S) at the tip of a single nerve fiber advanced through the tissues of the tail fin, its progress being shown from 10:30 A.M. to 4:00 P.M. At the end of one hour it had traveled about 45 micra; at the end of two hours 85 micra; and at the end of five and one-half hours 220 micra. (The dotted line in the final sketch indicates that a part of the fiber has been omitted from the drawing.) A second growing tip (T) followed the line laid down by the first.

Retraction is initiated first by the transformation of a growth cone into a retraction club, and then by a regressive flow of neuroplasm proximally (Fig. 3). A fine pointed axial filament is often left for a time; then this is withdrawn. Sometimes a vigorous production of transient knob-like excrescences accompanies the retraction. These resemble similar excrescences that often characterize cells dividing by mitosis.

The speed of retraction varies greatly. Over a brief period the amount of retraction sometimes exceeds the rate of one micron per minute, as in the case illustrated (Fig. 3). Usually, however, the rate of retraction is not so great.

It is possible to induce conditions experimentally which alternately favor growth and retraction. The example given (Fig. 4) shows how variations in the degree of chlorotone anesthesia are effective in bringing about conditions which favor alternately retraction and growth.

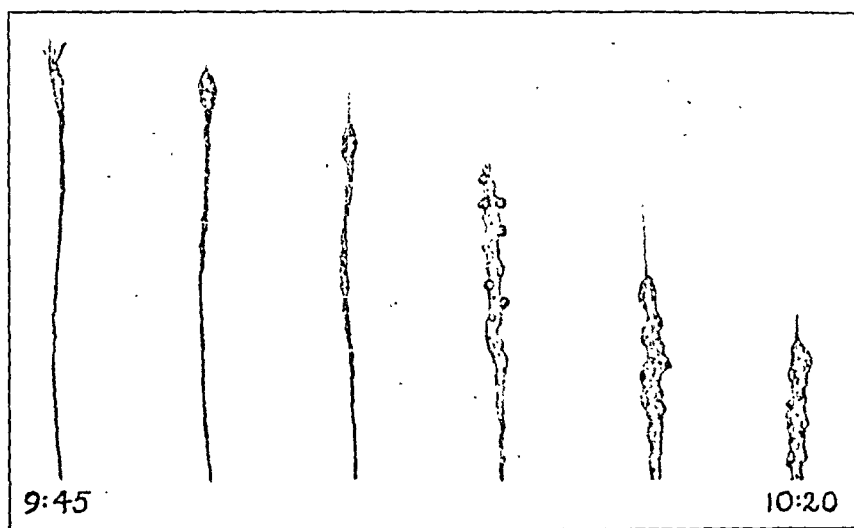


Fig. 3—Rapid retraction of the tip of a regenerating nerve fiber. An active growth cone advancing through the tissues at 9:45 A.M. became transformed into a retraction club and then vigorously retracted. At 10:20 A.M. it was in the position shown, having retracted about 45 micra.

In an earlier investigation^{3,†} I have described similar instances in metrazol-treated tadpoles.

As an ending recovers and grows out again after a period of retraction, it may, or may not, follow its former course. Case histories which illustrate each of these possibilities have been presented in a previous paper which described nerve ending reactions in tadpoles subjected to alcoholic intoxication.^{3,e}

CHANGES IN THE ENDINGS OF THE TERMINAL ARBORIZATION OF MYELINATED FIBERS DURING NORMAL GROWTH

In general, as a tadpole grows in size the clusters of cutaneous nerve endings of myelinated fibers also grow. Although the majority of the endings of a cluster are directed superficially toward the skin, a few may be directed deeply. Aberrant deep sprouts of this type which are of no service as cutaneous endings undergo readjustment along one of the following lines: they may advance further through the tissues and then extend superficially to establish cutaneous connections; they may retract variable distances and then change their direction of growth to reach the skin; they may suffer a variable amount of degeneration or autotomy with subsequent growth to a superficial position; or, finally,

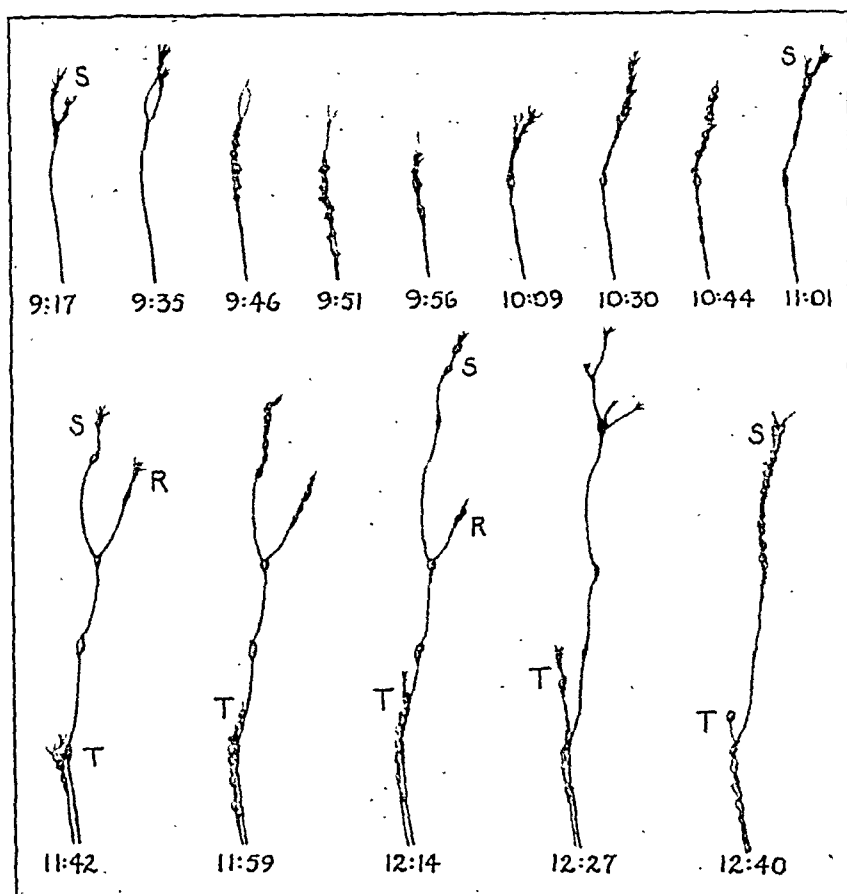


Fig. 4—Successive retraction and extension of regenerating nerve endings, correlated with treatments with strong and weak chlorotone solutions. An active pioneer growth cone (S) and a second growth cone (T) were watched in a tadpole under chlorotone anesthesia from 9:17 A.M. to 12:40 P.M. Strong chlorotone treatments were given from 9:37 to 9:53, from 10:33 to 10:53, from 11:49 to 12:07, and from 12:29 to 12:40. At other times over the period illustrated the tadpole was immersed in either pond water or very weak chlorotone solution. Typical retraction stages followed each of the four strong chlorotone treatments; as at 9:46 and 9:51, at 10:44, at 11:59, and at 12:40. Typical growth stages characterized the other periods while the tadpole recovered in pond water or in weak chlorotone. Before 11:42 a second growth cone (T) grew into the field illustrated, following the line of the pioneer fiber. A short branch (R) was present for about one hour, but retracted fully before 12:27.

they may be completely eliminated by either full retraction or autotomy.

I have obtained several complete case histories of the changes in entire trees of nerve endings while the frog tadpole grew markedly in size over a period of a month.* The example given here illustrates the

* Details of these have now been published in the *J. Comp. Neurol.*, 1942, 76:57.

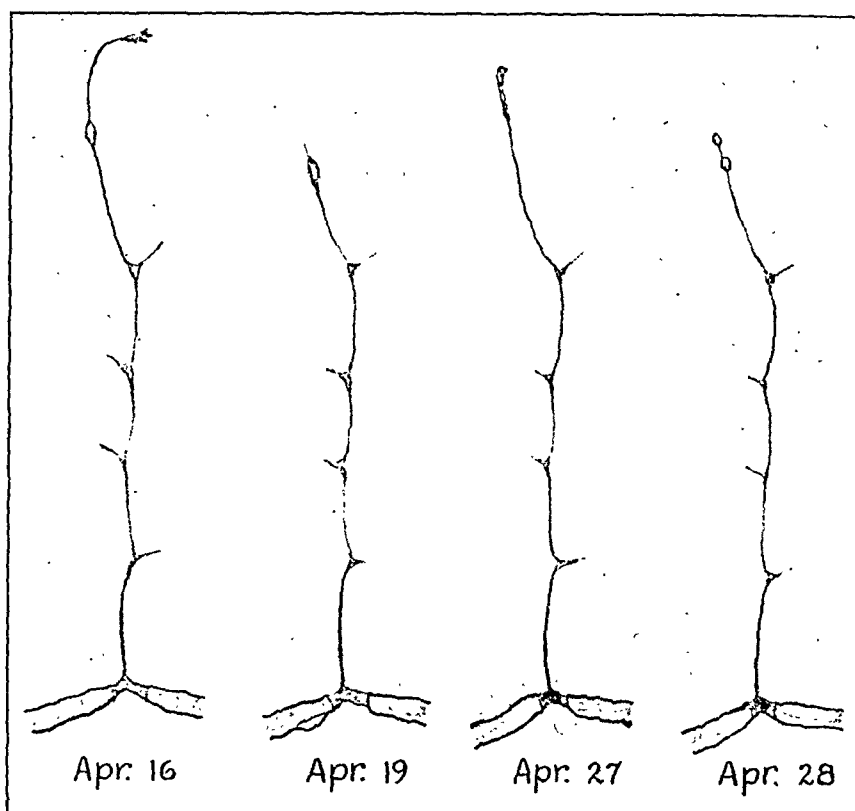


Fig. 6—Successive retraction and extension of a nerve ending correlated with successive periods of starvation and good nutrition. A motion picture record of this case was obtained. On April 16th a nerve ending with growth cone tip was observed slowly advancing. After three days of starvation definite retraction had taken place. On April 19th a typical retraction club was present at the tip. From April 20th to 27th food was made available and the ending again advanced. A second period of starvation was followed by a second retraction on April 28th.

changes of only two of the endings of a terminal arborization (Fig. 5). These are sufficient, however, to indicate that extension, retraction, branching, and elimination of branches all may take place during normal growth. They indicate further that a gradual increase in nerve ending extent is correlated with the increase in the growing terrain, and that a marked decrease in nerve ending length finally results when the tail fin undergoes reduction in size as metamorphosis starts.

Nerve endings often reflect general growth conditions. They are markedly influenced by variations in nutrition. Thus, in two tadpoles in which end arborizations were under observation for several weeks it was noted that a complete change of aquarium water and food mate-

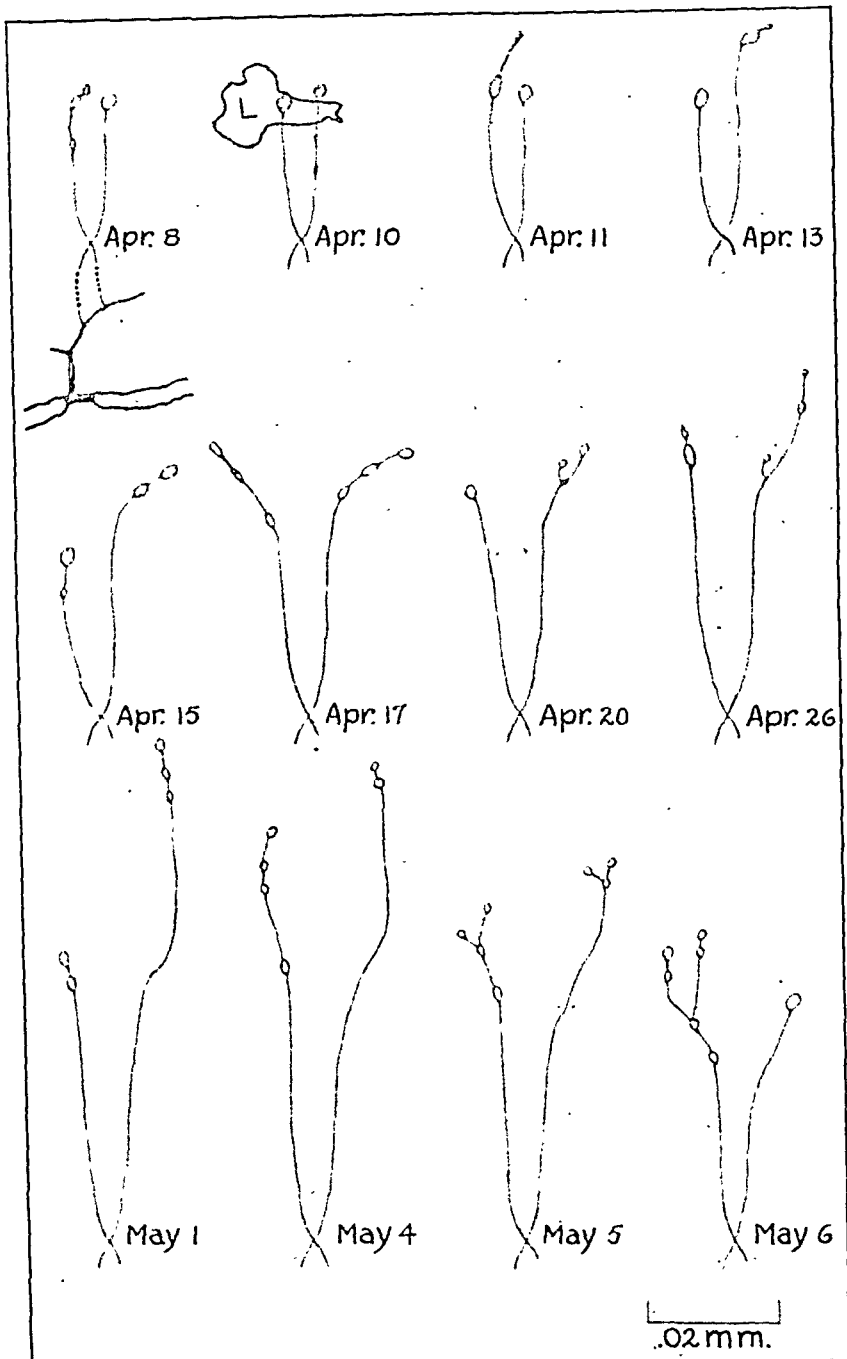


Fig. 5.—Adjustments of two nerve endings over a period of four weeks during marked growth of the tadpole. The sketches are made exactly to scale from motion picture records. A distance of 0.02 mm. (20 micra) is indicated below. During the period from April 8th to May 6th, the ending exhibited extension, retraction, and branching. On April 10th a leukocyte (L) approached and pressed against the ending at the left. Extension of this ending occurred shortly afterward. The final reduction in length of the endings from May 4th to May 6th was correlated with reduction in the size of the tail fin, as the tadpole began metamorphosis. (The dotted lines in the first sketch indicate that some of the nerve fiber length has been omitted from the drawing.)

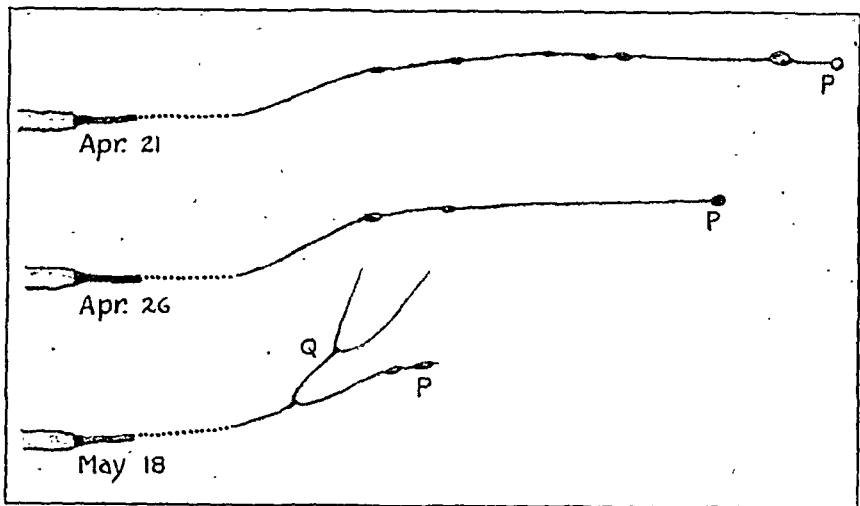


Fig. 7—Nerve ending retraction and new branch formation correlated with starvation succeeded by good nutrition. A motion picture record of this case was obtained. From April 18th to April 26th a tadpole was deprived of food; thereafter food was made available. A nerve ending (P) retracted about 18 micra during the period from April 21st to 26th. After that, in spite of the fact that food was made available, retraction continued to the extent of about 60 micra. Proximally along the retracting ending, however, a new branch (Q) grew out. (The dotted line indicates that some of the length of the fiber has been omitted from the drawing.)

rials brought about a spurt of general bodily growth within a few days. In each of these animals the nerve endings under observation exhibited, likewise, marked growth during the same period. Conversely, if food conditions are not quite favorable enough to support general bodily growth in a young tadpole, nerve endings are likely to exhibit little or no growth. Individual branches of a terminal arborization may react independently. One ending may grow while another retracts.

Terminal arborizations of regenerating fibers develop in regenerating zones about two weeks after partial tail amputation. Myelination progresses rapidly at this time. Case histories of the changes in the nerve endings of such regenerating regions are quite similar to those of normal growth, although somewhat greater variation is displayed.

EFFECTS OF STARVATION ON NERVE ENDINGS

Starvation causes general changes in the tissues of the tadpole's tail. Epithelium, muscle, connective tissue, and nerve all exhibit definite irritative changes. Nerve endings may undergo swelling, retraction, autotomy, and degeneration. Examples of each of these have been observed.

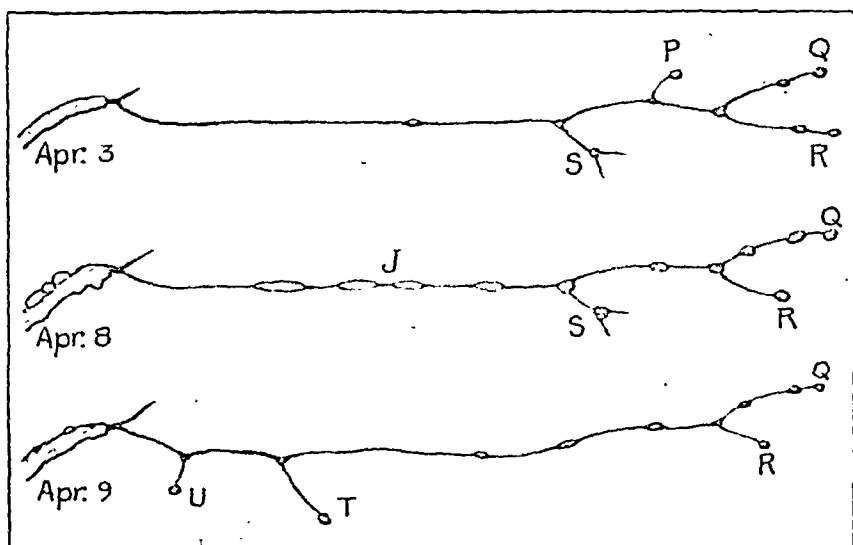


Fig. 8—Some changes in nerve endings correlated with alcoholic intoxication. Tadpole subjected to 3% alcohol for 47 minutes on April 3rd and again for 95 minutes on April 8th. Nerve ending, P, was eliminated after the first treatment. Ending, S (with its two sub-branches which are not fully shown in the drawing), was eliminated after the second treatment. Ending, R, underwent some retraction. New branches, T and U, appeared after the second treatment. Marked uneven swelling of the fiber also was visible in the region of J, on April 8th; also at Q, R, and S.

Young tadpoles are particularly responsive to alternating periods of starvation and good nutrition. Their nerve endings display regressive changes alternating with progressive changes. In the example given (Fig. 6) successive advance and retreat of a nerve ending were induced. This was correlated with the general nutritive conditions. While exact correlation was not found for all individual nerve endings in cases of this type, it was quite obvious that starvation brought about general regressive changes in both nerve fibers and their endings.

The other case cited (Fig. 7) indicates that regressive change in an ending initiated by starvation may continue, as regards that particular ending, even after good nutrition is restored. The recovery in this case was shown by the development of a new branch some distance proximally to the retracting ending.

A nerve ending in another starved tadpole formed the subject of an interesting motion picture record. As the picture was being taken, a greatly swollen end bulb underwent autotomy, after which it was ingested by a phagocytic leukocyte, while a new abortive growth cone appeared at the new tip of the nerve ending.

SOME CHANGES IN NERVE ENDINGS CORRELATED WITH ALCOHOLIC INTOXICATION

Frog tadpoles, immersed in weak solutions of alcohol for suitable periods of time, become slightly dazed. Their nerve fibers and nerve endings exhibit conspicuous changes. These changes have been described elsewhere in some detail with illustrations of many individual case histories.^{3,6} Myelinated fibers exhibit vacuolation, fibrillation of the axis cylinder, swelling, progressive separation of axis cylinder and myelin sheath, globule formation, and in extreme cases complete degeneration of some myelin segments with or without degeneration of the corresponding length of axis cylinder.

The cutaneous nerve endings exhibit swelling, retraction, and degeneration with or without autotomy. Sometimes retraction is sufficient to bring about elimination of a branch. During the recovery period following alcoholic intoxication, irritated endings may exhibit reduction of swelling, extension, and the formation of new branches. Endings of the fiber illustrated (Fig. 8) exhibit swelling, retraction, elimination of some branches, and formation of other new ones. A normal end bulb is in the gel state. With increasing irritation an end bulb changes progressively from the gel state toward the sol state; with recovery it returns to the gel state.

The effects of alcohol on growing nerve sprouts during rapid regeneration are even more striking. I have taken motion pictures of growth cones as they are transformed into retraction clubs which then rapidly retreat. With restoration of normal conditions the retracting nerve tips within a short time develop new growth cones and resume their advance through the tissues. They may proceed along their former course or along a new path. Examples of each have been observed and recorded ciné-photomicrographically. Rapidly regenerating nerve tips exhibit in somewhat exaggerated fashion the same fundamental changes shown by the resting nerve endings of terminal arborizations.

THE NEURILEMMA IN RELATION TO THE DUPLICATION OF AN ORIGINAL NERVE PATTERN BY A REGENERATING FIBER

An important question in the regeneration of a nerve fiber and its endings concerns the extent to which exact duplication of an original pattern may be expected. Several case histories of experimental nerve

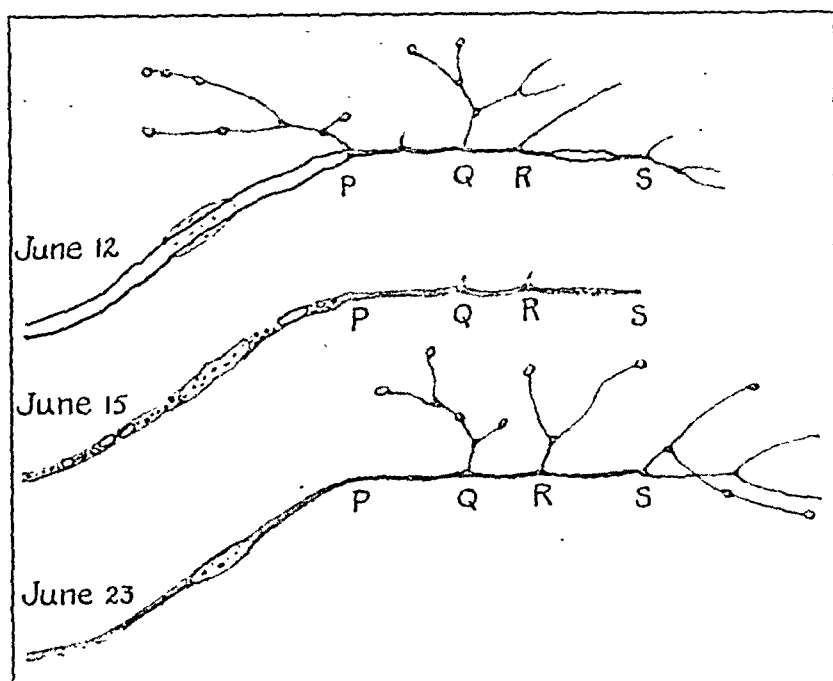


Fig. 9—The neurilemma as a directing factor during nerve regeneration in the exact duplication of an original pattern. On June 12th a nerve fiber ended as shown with branches at P, Q, R, and S. The fiber was then sectioned some distance proximally. On June 15th degenerating remnants of the fiber were still visible within the neurilemma. The neurilemma was visible as far distally as S with short funnel-like extensions at Q and R, though not at P. On June 23rd the regenerating fiber had grown back into the old neurilemma and had given rise to a set of endings at Q, R, and S. Exact duplication of the original nerve pattern corresponded only to the part enclosed by neurilemma. The pattern of branching of the fiber not ensheathed by neurilemma was unlike the original pattern. Collateral branches appeared at Q and R, but not at P, a result possibly correlated with the presence or absence of neurilemma side extensions at these points (cf. also Fig. 10).

section and of spontaneous degeneration and regeneration of fibers under observation have yielded clear-cut data on this point. The example given (Fig. 9) shows that a regenerating fiber growing within the old neurilemma tube duplicated the original pattern only as far as the neurilemma extended. Any branches that arose distally to this were naked and their pattern of branching bore no special resemblance to the original pattern.

Other case histories have given similar results. The inference is clear that the patterns of free unsheathed nerve endings which suffer degeneration are not exactly reproduced by regenerative processes. This fea-

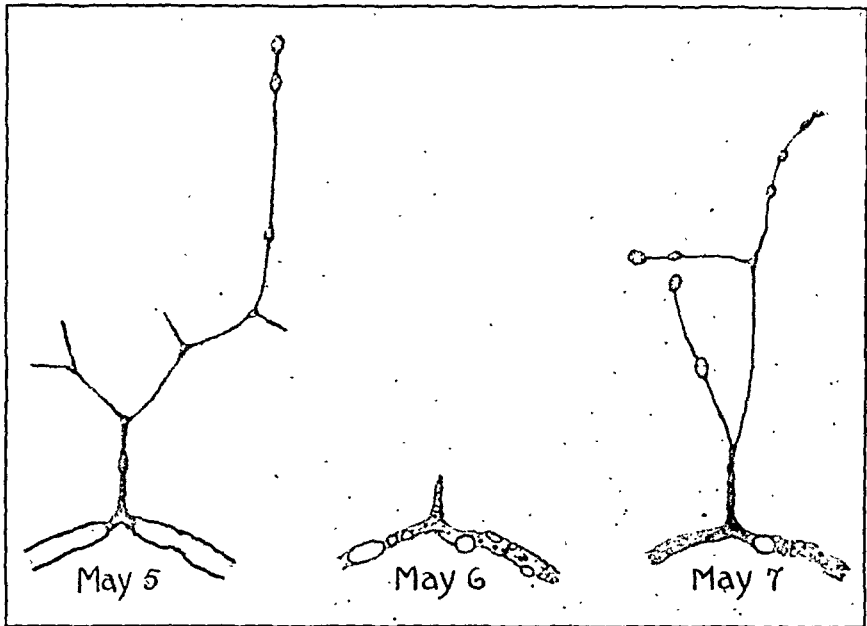


Fig. 10—Severe injury of a nerve fiber by metrazol treatment, with degeneration of a collateral branch with its cluster of endings followed by regeneration of a new collateral with a new pattern of endings. A motion picture record of this case was obtained. On May 5th a collateral of a myelinated fiber at a node of Ranvier branched as indicated. (The drawing shows the tip of only one of the branches.) Metrazol was administered in strength sufficient to induce degeneration of the entire collateral branch, as well as a short length of the main myelinated fiber. On May 6th the neurilemma sheath was present filled with degenerative debris of the fiber. On May 7th the main fiber had regenerated and given rise to a collateral at the former node of Ranvier site. Three endings developed on the collateral. The pattern of branching, however, was quite unlike that of the original pattern before the injury.

ture of nerve ending regeneration is of decided significance in connection with the question of synapse stability in the central nervous system, a problem to be discussed below in this paper.

DEGENERATION AND REGENERATION OF NERVE ENDINGS IN METRAZOL-TREATED TADPOLES

Profound alterations become visible in the tissues of metrazol-treated tadpoles. The circulation is markedly affected. It may stop temporarily in the small vessels near the edge of the tail fin. Muscle, epithelium, and nerve all exhibit structural changes.

The nerve changes are of special interest. They afford a basis for the interpretation of certain results that have been obtained in the treat-

ment of human mental disorders by injections of metrazol. In a previous paper^{3,6} I have described the results of subjecting tadpoles to mild, moderate and severe treatments with metrazol. Case histories have been presented which illustrate nerve fiber recovery after various gradations of irritation and injury. One example is offered here (Fig. 10) of the degeneration of a cluster of endings after severe metrazol treatment, followed by regeneration of a new group of endings with a different pattern. In this case the metrazol treatment caused elimination of an entire terminal arborization. It also caused degeneration of several of the most distal myelin segments of the main fiber as well as some of the corresponding axis cylinder. Nevertheless, regeneration quickly ensued. A new sprout grew out from the main fiber at the place of the original collateral. Its manner of branching, however, bore no resemblance to the pattern of the original arborization. This case, like that of Fig. 9, indicates that the patterns of free unsheathed nerve endings which undergo degeneration are not exactly duplicated by regenerative processes.

REACTIONS OF NERVE ENDINGS IN TADPOLES SUBJECTED TO ELECTRIC SHOCKS

One of the best means of bringing about alterations in nerve ending patterns is through the use of electric shocks of suitable strength and number. Along with metrazol and insulin treatments for certain human mental diseases, the electric shock therapy has been gaining favor. Observations of nerve ending reactions to electricity in tadpoles, therefore, are of particular interest because of their possible application to nerve ending changes at synapses in the brain of human mental patients following electric shock treatments.

I have subjected tadpoles to various degrees of electrically-induced injury. Excellent case histories have been obtained of nerve fibers and their endings as these suffer injury and then recover. The example given (Fig. 11) shows a swollen nerve fiber on the day following a fairly severe series of electric shocks. One small branch underwent degeneration. Another ending, though somewhat swollen, readily recovered and grew out into new territory.

Other case histories of electric shock injury and recovery indicate that loss of nerve substance may be much greater in extent. In extreme cases an entire collateral may suffer degeneration, as in the metrazol

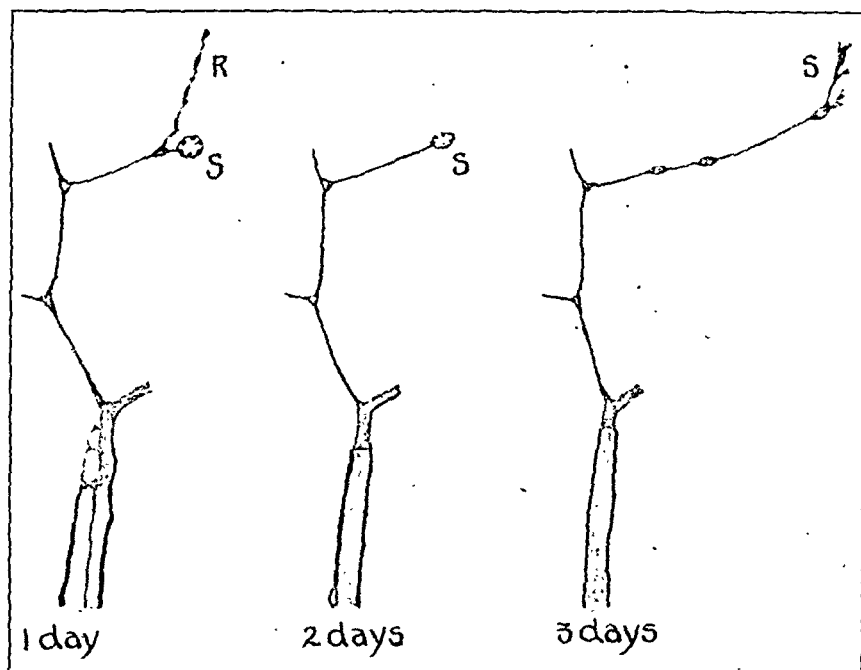


Fig. 11—Elimination of one nerve ending, and swelling and extension of another following electric shock treatments. On the day following a series of electric shocks a myelinated fiber was noted in greatly swollen condition. One ending (S) exhibited swelling. Another short branch (R) was in process of degeneration. On the next day (i.e., two days after the electric shocks) the myelin segment was almost normal; the ending (S) was less swollen; and the ending (R) was gone. On the following day S had advanced markedly and was provided with a growth cone.

case cited above (cf. Fig. 10). In one rather interesting case the electrical treatment was just strong enough to induce degeneration of several myelin segments of a fiber. The enclosed axis cylinder, however, survived although its endings suffered marked reduction with complete elimination of some. During the recovery period of the next few days new branches developed. Further details of electric shock experiments will be published in a separate paper.*

CHANGES IN NERVE ENDINGS OF THE DISTAL STUMP AFTER SECTION

After a myelinated fiber is cut typical degenerative changes quickly become discernible in the endings which belong to the distal stump. In the example given (Fig. 12) within the first hour swelling of the endings was noticeable. Retraction, granulation, and liquefaction also took place. Later the branches became exceedingly tenuous and began to fragment.

* This paper has now been published in the *Proc. Am. Philos. Soc.*, 1942, 85:163.

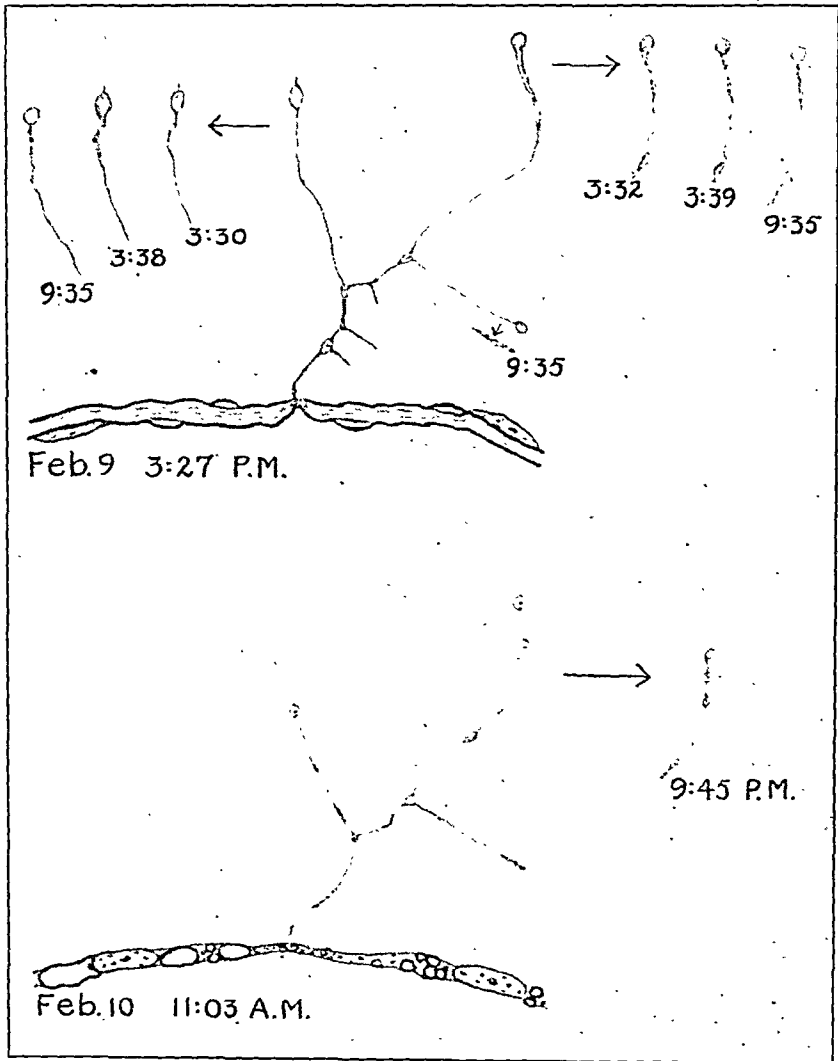


Fig. 12—Degenerative changes in nerve endings after nerve section. On February 9th at 3:03 P.M. a myelinated nerve fiber was cut at a point some distance proximally to the part illustrated. At 3:27 P.M. distinct changes in the nerve endings of the collateral branch were discernible. The ending at the left exhibited swelling and retraction club formation; the ending at the right exhibited swelling and thickening. Other changes became visible during the next six hours at the times indicated. On February 10th at 11:03 A.M. the three endings of the collateral branch were still visible. At this time the collateral was exceedingly tenuous. Myelin degeneration was visible. At 9:45 P.M. the short length of fiber sketched at the right was all that was left of the entire collateral. No trace of this was visible on February 11th.

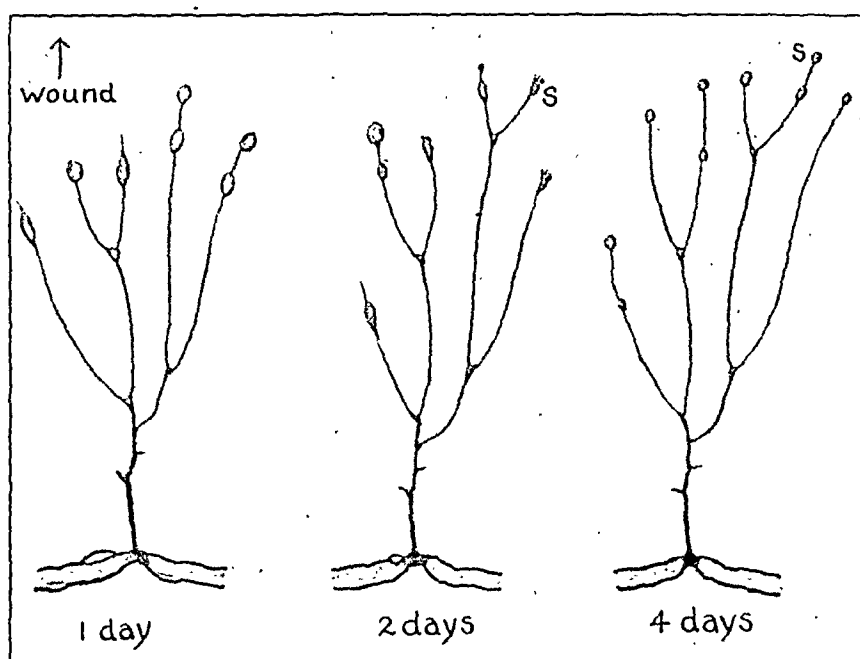


Fig. 13—Response of nerve endings near a wound during subsequent tissue regulation and repair. During the first day after a minor wound infliction a group of nearby nerve endings exhibited swelling and slight retraction. After two days growth cones were present on some of the endings. A new branch (S) was present. One ending, however, still exhibited swelling and one had retracted. After four days several endings had advanced toward the zone in which tissue repairs were taking place. All endings at this time were in the resting state.

It is clear that these degenerative changes in endings belonging to the distal stump bear a decided resemblance to the various irritative changes in endings, such as have been pointed out in many of the experimental treatments described above. In other words, the early changes in an irritated ending which is destined to recover are much like the early changes in a degenerating ending which is destined to be lost completely.

CHANGES IN NERVE ENDINGS NEAR A WOUND AS CELLULAR REGULATION AND REPAIR ENSUE

If a local wound is made in the tadpole's tail by cutting, bruising, or other means, irritation of nearby nerve fibers takes place. Typical irritative changes of swelling and retraction may be seen readily in favorable cases. If the nerve endings under observation are too close to the wound, or if the wound becomes too extensive, complete degenera-

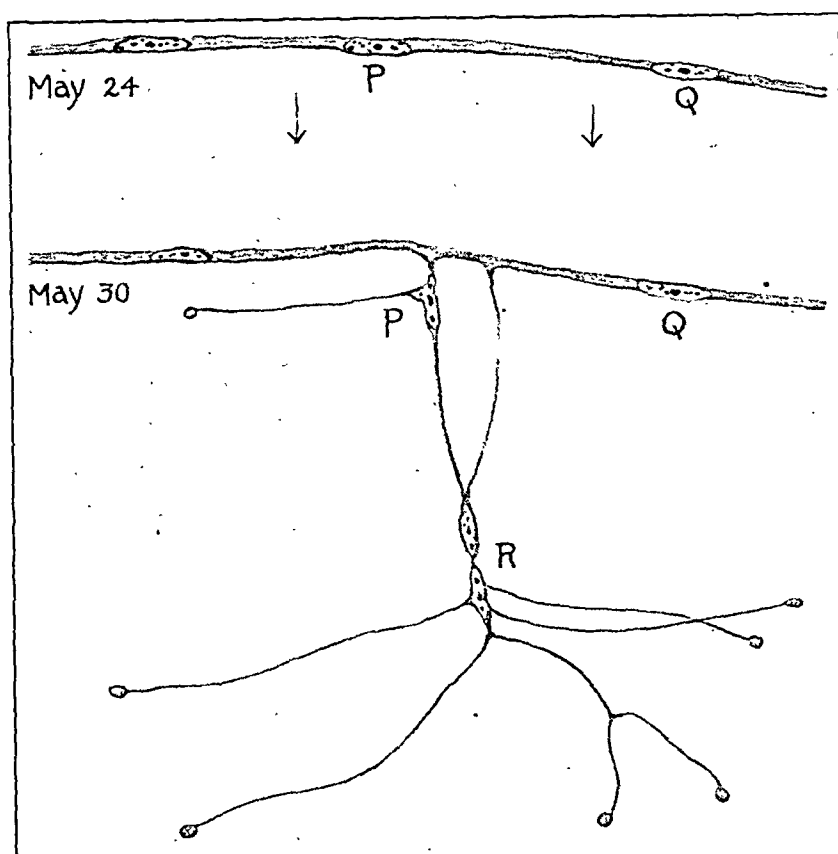


Fig. 14—The origin of collateral sprouts from a nerve following experimental denervation of an adjacent zone. On May 24th by appropriate sectioning of the tadpole tail fin a zone in the direction of the arrows was deprived of its nerve supply. The nerve figured was at the edge of the denervated region. Two new side sprouts arose, one on May 27th and one on May 28th. These grew and by May 30th had given rise to seven endings which supplied a part of the denervated zone. P, Q, and R mark the positions of neurilemma sheath cells. (The two sheath cells at R arose by division from a sheath cell which transferred from a degenerating nerve in the denervated zone.)

tion of endings may ensue. On the other hand, if the wound is too slight or if the endings are too distant, little or no change is visible. In suitable cases, however, excellent case histories of regressive and progressive changes in nerve endings from day to day may be obtained. In the example cited (Fig. 13) the endings of a terminal arborization exhibited definite swelling and retraction during the early period of injury. This was followed by recovery with growth and branching as wound repair proceeded.

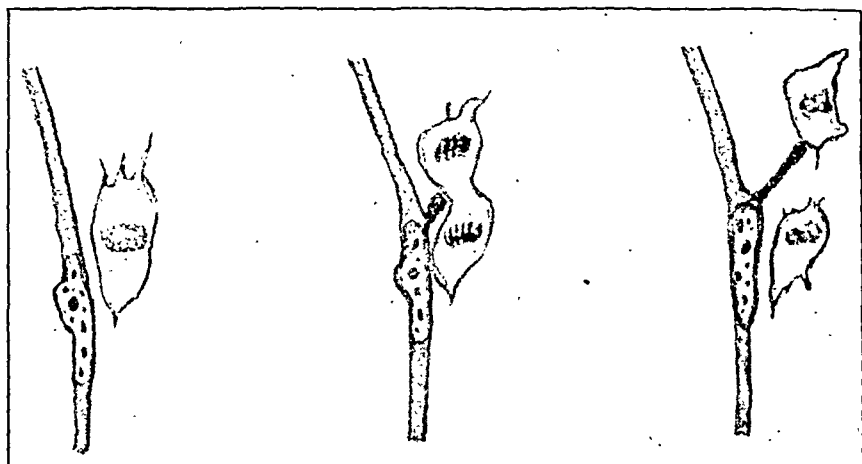


Fig. 15—Origin of a nerve sprout correlated with mitosis of a nearby myoblast. A motion picture record of this case was obtained. A young muscle cell in division was located close to a small unmyelinated nerve and sheath cell. Immediately after the metaphase of mitosis a knob-like bulge appeared at the side of the nerve. This rapidly grew out as a new nerve branch, the tip remaining in contact with one of the daughter cells.

EVOCATION OF COLLATERAL SPROUTS FROM A NERVE FOLLOWING EXPERIMENTAL DENERVATION OF ADJACENT TERRITORY

Obliteration of the nerve supply for a region quickly sets in motion recovery processes that will ultimately lead to the restoration of innervation of the affected region. An important feature of such recovery processes is the response of the nerves nearest the denervated zone. These may give rise to new sprouts which then quickly grow into the denervated territory. Presumably in some manner the denervated zone constitutes a local stimulus with sufficient influence to evoke new sprouts from nearby fibers which otherwise would not have given rise to them. In the example given (Fig. 14) a period of three days was enough to elicit the first new collateral branch from the adjacent nerve.

NERVE FIBERS AND ENDINGS AS AFFECTED BY DIVIDING CELLS

Many instances have been recorded in which a nerve fiber exhibited definite changes during the division of a cell in close proximity. In one case (Fig. 15), as a young muscle cell divided by mitosis a new sprout arose from a nearby unmyelinated fiber. The sprout arose at a time of great agitation, namely, immediately after the dividing cell passed

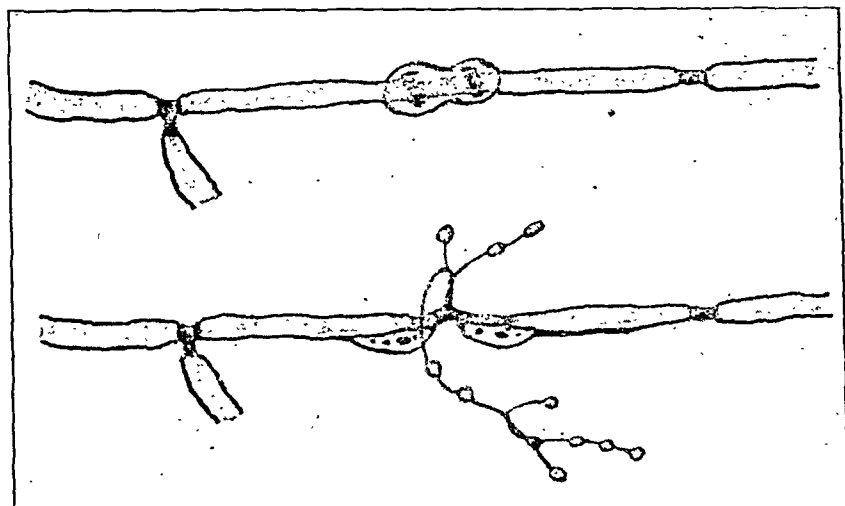


Fig. 16—Origin of a collateral set of endings from a myelinated fiber following sheath cell mitosis. In a young tadpole a sheath cell belonging to the penultimate myelin segment of a fiber underwent mitosis. The myelin became divided into two segments, each with a daughter sheath cell. Three hours after the mitosis a new young cluster of endings was visible, arising from the main fiber at a point between the two daughter sheath cells.

the metaphase stage. At this time the whole locus was in a state of activity, a feature clearly revealed by the fast motion ciné-photomicrographs that were obtained.

A dividing neurilemma sheath cell also constitutes a stimulus for the origin of new collateral nerve sprouts. I have watched several examples, including both myelinated and unmyelinated fibers, in which new branches arose following the metaphase. Motion pictures of dividing neurilemma cells vividly demonstrate that at such a time the nerve fiber swells and becomes more plastic. It is certainly stimulated mechanically, and possibly chemically, by the dividing cell. The case selected here for illustration (Fig. 16) shows the origin of a new collateral branch after mitosis of a neurilemma cell associated with a myelin segment.

Neurilemma cells also play a part in aiding regenerating nerve fiber tips to get past obstacles. Such aid is sometimes accompanied by mitotic division of the neurilemma cell. Examples of this have been presented in previous papers.^{3,a,b,d}

Connective tissue cells in division may also cause activity of nerve endings provided they are in close juxtaposition. In two cases I have

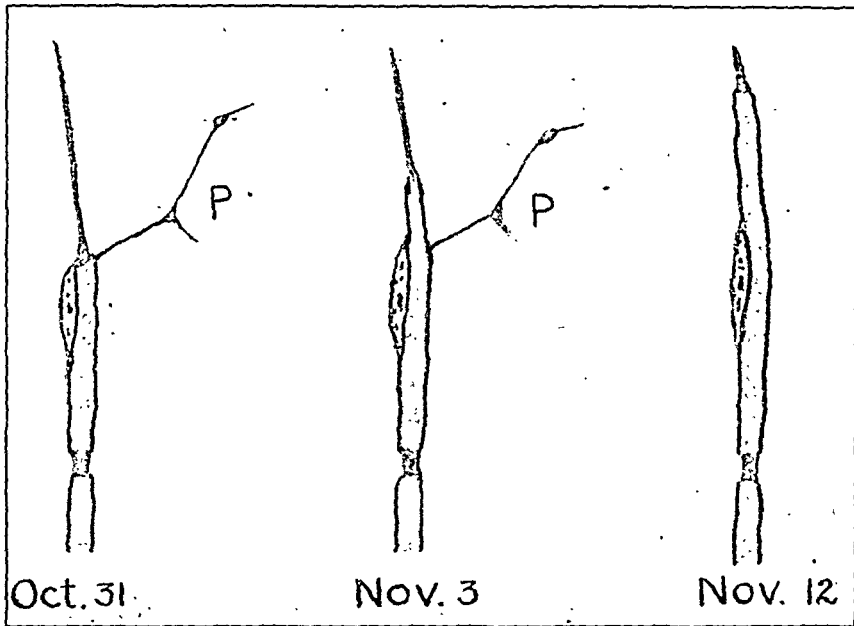


Fig. 17—Elimination of a collateral branch by advancing myelination. On October 31st a side branch (P) was present at the end of a terminal myelin segment. During the next three days the myelin advanced beyond the side branch, as indicated. By November 12th the side branch had become entirely eliminated.

seen a nerve ending of resting type become transformed into one of growing type, as a result of the motion of a contiguous dividing connective tissue cell. In one case the nerve ending tip advanced a short distance. In the other case there was no advance; after a brief period of activity characterized by slow movements of delicate pseudopods, the nerve tip again became transformed into the resting type with spherical end bulb.

MYELINATION AS A FACTOR IN ELIMINATION OF NERVE ENDINGS

Myelination accompanies the growth and maturing of nerve fibers. One feature of this is the increase in the size and complexity of many of the terminal arborizations. Nevertheless, another important aspect of myelin sheath formation is the complete elimination of some collateral branches with their endings. I have observed many cases of this. In the example given (Fig. 17), a collateral branch was eliminated during growth of a myelin segment. In a previous paper^{3, b} I have illustrated a similar elimination of a much larger collateral side branch

which had itself become ensheathed with a myelin segment.

The myelination process, however, does not always eliminate collateral branches which are not located at nodes of Ranvier. I have followed the histories of many such internodal collaterals and noted their survival up to the time at which metamorphosis took place.

MISCELLANEOUS OBSERVATIONS

A few other observations of nerve ending adjustments may be mentioned briefly. Typical regressive changes in nerve fibers and their endings have been induced by heat (37° - 40° C.) and cold, by relatively weak hypertonic sodium chloride solutions, by X-rays, by insulin extracts, and by foul aquarium water in which putrefaction is occurring. Recovery takes place after such irritants provided the injury is not too great.

Circulatory disorder is usually associated with nerve irritation. Chloretone, alcohol, metrazol, insulin, electric shocks, and hypertonic salt solutions all cause a slowing of the circulating blood. Nerve ending changes follow. Rarely, as in one case of chloretone treatment, an advancing growth cone of a regenerating fiber continued its activity and advanced an appreciable distance after the circulation in the entire tail had ceased.

As the time for metamorphosis of the frog tadpole approaches, the tail fin suffers increasing reduction in size. Irritative and degenerative changes become apparent in all of the tissues. Nerve fibers and their endings become affected. The nerve endings exhibit swelling and may suffer some retraction. Occasionally, however, growth and extension of an ending is visible even in a markedly reduced tail fin.

Connective tissue cells often block advancing nerve endings. Prolonged blocking may lead to nerve autotomy. Blocking of a rapidly regenerating nerve fiber tip may be followed by retraction and growth in a new direction, or by retraction and branching with growth of the branches in new directions past the obstruction.

CINÉ-PHOTOMICROGRAPHS OF NERVE ENDING ADJUSTMENTS

Ciné-photomicrographs of both normal and fast motion types have been obtained directly from living tadpoles. These record the typical changes in nerve endings under ordinary conditions and under conditions of irritation, injury, and recovery. Fast motion ciné-photomicro-

graphs are particularly valuable in revealing slow tissue changes. Prolonged day-to-day case histories are suitably shown by pictures taken at the normal rate. The motion pictures exhibited include, in addition to changes in nerve fibers and nerve endings, the activities of some other cells which are associated with nerve ending adjustments.

The subjects of some of the pictures follow.

1. Rapidly growing nerve tip blocked temporarily by a connective tissue cell process.

2. Rapidly growing nerve tip advancing through the tissues after passing a blockade formed by two connective tissue cells.

3. Two growth cones diverging as they advance.

4. Retraction of a growth cone (two examples).

5. Retraction of an actively advancing nerve tip induced by alcohol treatment, followed by resumption of growth along a new route with the restoration of normal conditions.

6. Reactions of the myelin sheath, axis cylinder, and nerve endings during and following alcohol treatments.

7. Swelling, retraction, recovery, autotomy, and degeneration of nerve endings in alcoholized tadpoles.

8. Degeneration of an entire cluster of nerve endings caused by severe metrazol-induced injury, followed by regeneration of a new nerve ending pattern at the former site.

9. Epithelial cells (overlying irritated cutaneous nerve endings) displaying rapid movements of readjustment, three hours after metrazol treatment.

10. Lymphocyte movements within the neurilemma of an adjusting nerve trunk after metrazol injury.

11. Continuous, though slow, advance of a cutaneous ending over a four day period in a tadpole nearing metamorphosis.

12. The retraction of an ending, initiated by starvation, continuing even after normal food conditions have been restored.

13. The genesis of a nerve branch in close proximity to, and probably stimulated by, a dividing myoblast.

14. Nerve adjustments associated with division and movements of sheath cells.

15. Growth of fibroblast process following fibroblast mitosis (for comparison with nerve tip growth).

16. Markedly swollen nerve endings on the day following severe

electric shock treatments.

17. Electrical injury of nerve endings with swelling and degeneration, followed during the next four days by nerve ending extension and establishment of new connections.

18. Clotting at the muscle-tendon junction of a fiber of striated muscle during electrical injury.

19. Two case histories showing successive retraction and advance of the same individual nerve endings, correlated with alternating periods of starvation and good nutrition.

20. Chronic swelling and autotomy of an end bulb of a fiber in a starved tadpole, followed by development of an abortive growth cone tip.

21. Comparison of macrophage activity during ingestion of a swollen degenerating nerve ending and during ingestion of an extravasated red blood cell.

DISCUSSION

A few points suggested by the foregoing observations may be discussed briefly. It is clear that while there are many varieties of irritation and injury, nerve fiber endings display only one general pattern of changes. This includes swelling, retraction, and variable amounts of degeneration. Likewise, the changes during recovery follow one general pattern. This includes reduction of swelling, growth and branching of endings, and the establishment of new terminal positions.* The point has already been made that the end arborizations are free and unsheathed. There is, therefore, no duplication of an original pattern of nerve endings as a part of the recovery process following a period of regressive change. This feature makes for flexibility. Nerve endings are not absolutely fixed and stable. They adjust themselves to changing stresses and strains.

It should be emphasized that my observations deal only with free unsheathed endings, peripherally located. This type, however, is present in enormous numbers in the central nervous system, taking part in the synapses between nerve cells. Cajal^{1,4} has given us many illus-

* Nerve endings represent the part of the nerve cell that is most distant from the cell nucleus. In general, it is true of cells having long processes that the most peripheral parts suffer regressive change first. I have watched irritated connective tissue cells, pigment cells, and the endothelial cells of blood and lymph capillary sprouts. During the phases of irritation and recovery, the tips of the processes of these cells exhibit changes much like those of nerve endings. The behavior of the nerve endings, therefore, is not unique.

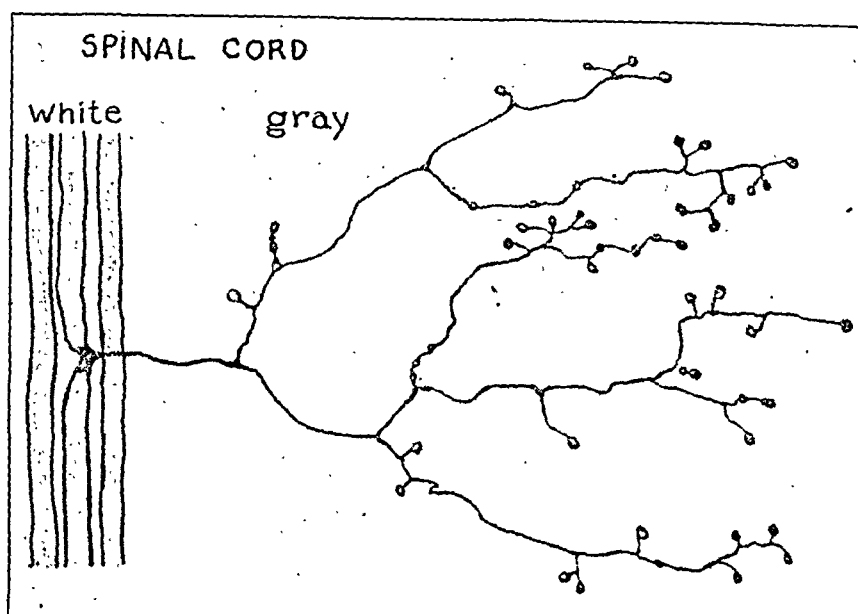


Fig. 18—A terminal arborization of nerve endings in the gray matter of the cat's spinal cord, arising from a collateral branch of a myelinated fiber in the white matter. Redrawn from Cajal, representing two illustrations combined. This illustration of synaptic nerve endings in the central nervous system is strikingly similar to that of peripheral nerve endings at the skin (cf. Fig. 1).

trations. In the example reproduced here from the cat's spinal cord (Fig. 18) is shown a collateral branch with its terminal arborization in the gray matter. This tree of free nerve endings is quite like those in the frog tadpole which have formed the subject of my investigations. Similar end arborizations are present also in the brain.

Unfortunately direct observations cannot be made on nerve endings located within the central nervous system. Case histories of individual endings, therefore, have never been recorded. The fixed preparations of Cajal,¹ however, clearly show that a centrally located nerve ending does not always have a resting end bulb tip. It may have a swollen irritated tip, a growth cone tip, or a retraction club tip. Endings exhibiting degeneration and autotomy are also apparent.

Accordingly, there is little doubt in my mind but that the free nerve endings of the central nervous system may undergo changes during irritation, injury, and recovery much like those of peripherally located endings. This is significant because of the role such endings play at synapses. The conclusion seems justified that some flexibility in synap-

tic connections is possible; that certain changes may take place from time to time with the elimination of some old synapses and the establishment of some new ones.* I have already proposed such an anatomical mechanism as a basis to account for the changed mental outlook that sometimes occurs in metrazol-treated human beings.^{3,†}

Not all synapses are alike. In some cases there is extensive contact between the two nerve cells concerned through complex interlacing of their processes. In other cases there is relatively limited contact, the endings of one nerve cell merely touching at one or more places the endings, or processes, or cell body of the other nerve cell.** The former type of synapse would probably be more stable than the latter type.

Nerve fibers which supply striated muscle are usually ensheathed with neurilemma all the way to the muscle fiber end plate.⁷ Likewise, nerve fibers which end in special sensory corpuscles of the encapsulated type are usually ensheathed with neurilemma all the way to the corpuscle.⁷ Such endings would also be more stable than those of the free type. If injury did take place the surviving neurilemma would function to direct the regenerating fiber along the original path to the end structure concerned.

In conclusion, it seems probable to me that nerve ending changes accompany many bodily disorders of both acute and chronic types; such, for example, as during severe infectious diseases characterized by toxins and fever, during states of marked hormonal imbalance, during chronic vitamin deficiency, during marked circulatory and kidney disturbances, and during the gradual tissue degeneration that characterizes the approach of senility. In man, the synaptic changes in the brain probably would be of most significance in accounting for whatever mental changes might accompany such general bodily disorders.

SUMMARY

1. The nerve endings of terminal arborizations of myelinated fibers in frog tadpoles, though relatively stable, may undergo adjustments under both normal and experimental conditions. The principal changes exhibited are swelling, retraction, extension, branching, autotomy, and

* Extensive regeneration of nerve cells and fibers does not occur in the brain and spinal cord, as is well known. Nevertheless, Cajal² presents many illustrations which lead me to the conclusion that the delicate branches of terminal arborizations readily adjust themselves either progressively or regressively.

** I agree with the "contact idea" as to the nature of the synapse. Strong evidence for this has been presented recently by Bartelmez and Hoerr³ and by Bodian.⁴

degeneration. Essentially similar nerve ending adjustments result from slow chronic changes and from rapid acute changes.

2. During a period of general bodily growth, a terminal arborization increases in the size and number of its branches. From time to time individual endings may become swollen. They then may extend by growth cone activity, or retract, or suffer degeneration. Sometimes autotomy of a branch, or a part of a branch takes place. Some endings of cutaneous fibers are aberrant and grow in a deep, instead of a superficial, direction. Such branches become eliminated by retraction, or degeneration, or as further growth takes place they may change their course in such manner as to extend in a superficial direction.

3. Starvation induces regressive changes of swelling, retraction, and degeneration. Successive retraction and growth of the same individual endings may be induced experimentally by imposing on tadpoles alternating periods of starvation and good nutrition.

4. Treatments of tadpoles with alcohol or with chloretone may cause typical regressive changes in nerve endings. With such treatments alternating with recovery periods, regressive and progressive changes may be induced successively in individual nerve endings. The growth cone tips of rapidly regenerating nerve fibers are particularly susceptible to experimental modifications of this sort.

5. At rest the end bulb (bouton) at the tip of a branch is in the gel state. During irritation it undergoes increasing change toward the sol state as swelling ensues. During recovery it returns to the gel state. Retracting and growing tips are in an intermediate state.

6. During regeneration after injury, nerve fibers and their branches duplicate an original pattern only as far as they are ensheathed by the original neurilemma. Free unsheathed nerve endings, therefore, establish new connections during recovery.

7. Nerve fibers and their endings display marked changes of irritation and injury in tadpoles subjected to metrazol, or to insulin, or to electric shocks. With recovery after each of these treatments the patterns of individual nerve ending clusters may be quite different from the patterns before treatment.

8. Nerve ending changes are also apparent after treatments with hypertonic sodium chloride solutions and after exposure to moderate rise in temperature.

9. The changes in irritated or slightly injured nerve endings which

will recover resemble closely the early changes in nerve endings undergoing trophic degeneration which will not recover.

10. Local wounds sometimes stimulate adjustments of nearby nerve endings in uninjured territory. Swelling, retraction, extension, and branching of endings may result.

11. A denervated zone may evoke new side sprouts from nearby uninjured nerve fibers. Collateral innervation may thus be established.

12. New nerve sprouts sometimes appear on fibers that are contiguous to dividing cells (neurilemma cells, myoblasts, and fibroblasts). This takes place after the metaphase, during a time of marked agitation.

13. The advance of the myelin sheath on a fiber is a factor in causing elimination of some branches by retraction or autotomy. Even large branches with myelin segments are occasionally eliminated.

14. Free nerve endings which are present in large numbers in the central nervous system probably undergo adjustments similar to those of free cutaneous endings. Synaptic changes would be possible, therefore, from time to time. Thus, changes in brain synapse patterns might be brought about as a result of shock treatments, severe intoxications and fevers, and marked nutritional or hormonal imbalance. Such changes also probably accompany ordinary growth and maturation of the brain.

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THE DEVELOPMENT OF NEUROLOGICAL SURGERY IN NEW YORK CITY DURING THE PAST TWENTY-FIVE YEARS*

With Remarks on Advances due to Experiences in the First World War

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I N our city and country, neurological surgery began to be recognized as a special field only a little more than twenty-five years ago. Before that time and within the memory of some of us, forty to fifty years ago, operations upon the central nervous system were rare and were performed by the general surgeon. Some of the earliest operations for tumor of the brain were performed in New York City by general surgeons, Drs. Charles McBurney at Roosevelt Hospital, Arpad G. Gerster at The Mount Sinai Hospital, and Andrew J. McCosh at the Presbyterian Hospital. Just fifty years ago, in 1892, Frank Hartley described the operation for the intracranial exposure of the Gasserian ganglion which was known for many years as the Hartley-Krause operation.

It was natural that the neurologist of those days felt that he should supervise any operation on the central nervous system that was performed by the general surgeon. Not quite fifty years ago, in 1893, M. Allen Starr, Professor of Neurology at the College of Physicians and Surgeons, published a volume on the surgery of the brain. You will note the interesting fact that a book on brain surgery was written by a neurologist. In this book, Dr. Starr gave the following quaint advice to the surgeon: "It is an absolute requisite of success in cerebral operations that every detail of aseptic surgery should be carried out to perfection. It is useless to make elaborate preparations, to sterilize instruments and to apply antiseptic solutions to the hands, if in the midst of the operation the surgeon stops for a moment to adjust his septic eyeglass, or to

* Read at the combined meeting of the Section on Neurology and the New York Neurological Society, March 10, 1942. This paper was also in part read at a dinner to celebrate the 25th anniversary of the foundation of a neurological service at Bellevue Hospital.

blow his nose on a septic handkerchief without subsequently washing his hands again." This was perhaps good advice but Dr. Starr spoiled it all by his next remark: "By covering the hand with a wet aseptic towel, the surgeon can safely handle anything he desires." It is hard to realize that this crude advice was given less than fifty years ago.

Even as recently as seventeen years ago, the neurologist had the point of view expressed, for example, by Dr. Mills of Philadelphia, that one of the functions of the neurologist is to *superintend* and *direct* operative procedures on the brain and spinal cord by the surgeon.* At about the same period, a similar viewpoint was expressed to me in writing by another eminent neurologist: "that the function of the surgeon was to do the technical work and to make the opening in the skull or spine in the area mapped out by the neurologist, and that the surgeon should not attempt to make a diagnosis or to localize the growth." Fortunately, *tempora mutantur et nos mutamur in illis!* Fortunately, also, the neurological surgeon has learned something of neurology so that he is no longer looked upon merely as a technician. Perhaps the change may be appreciated by the evidence that in recent years an increasing number of neurological surgeons have been elected to membership in the American Neurological Association: Twenty-five years ago, in 1917, there were 121 active members in the Association of whom 4 per cent were neurological surgeons; in 1925, the percentage was 5; in 1935, it was 10 and in 1941, it was 15 per cent. This steady increase in the number of neurological surgeons in the American Neurological Association was a cause for perturbation of some of the members. One of them wrote to the Council of the Association and asked how long it would be, at the same rate of increase, before the American Neurological Association would consist mainly of neurological surgeons! When that letter was read at the Council meeting, one of the members calculated that at the same rate, in 1967, more than one-half of the members would be neurological surgeons!

A neurosurgical service can be developed only in a special hospital or in a general hospital in which there are special neurological and neurosurgical beds. A capable operating team cannot be developed in an institution in which a major operation upon the central nervous system is performed only a few times a year. In most of the general hospitals in New York City, until about twenty-five years ago, there

* Semi-Centennial Volume of the American Neurological Association, 1875-1924.

was not a sufficient number of patients with diseases of the nervous system to justify a special neurosurgical service. If the Neurological Institute (which is a special hospital) was excepted, there were at that period active neurosurgical services only at The Mount Sinai Hospital and at Bellevue Hospital in both of which there were special wards for patients suffering from diseases of the nervous system. Recently, departments for the surgical treatment of diseases of the nervous system have been developed at the New York, the Brooklyn Jewish and to some extent in a few smaller hospitals. Also, it is of interest to note that until recently, the title of the neurological surgeon—if he was a member of the faculty of a medical school—was “Professor of Surgery.” Dr. Cushing was professor of general surgery at Harvard and Dr. Frazier was professor of general surgery at the University of Pennsylvania although both limited their work almost exclusively to neurological surgery. However, about 21 years ago, Columbia University at the College of Physicians and Surgeons, established a full chair for neurological surgery with a seat on the faculty of the Medical School.

Neurological surgery has developed, as was logical, as an offshoot from general surgery, and the emergence was due to a process of education of the general surgeon, the neurologist, the physician and the layman. Actually it required only a few decades for the new specialty to be generally recognized. In the beginning, a few general surgeons began to devote themselves to neurology and to operations upon the nervous system. There is, perhaps, a certain disadvantage in what is happening today, i.e., that many young men receive their training in neurosurgery and become neurological surgeons without having had a thorough basic experience in general surgery. While it is true that a neurologist may learn to do his own operating (as was done by the late Ottfried Foerster in Breslau, Germany and by Clovis Vincent in Paris), a groundwork in general surgery is of no little value.

Most of the younger neurological surgeons of our day have received their training in one of the neurosurgical centers in this country. A few of the older ones began to practice in the special field after an experience with injuries of the brain, spinal cord and peripheral nerves in the first World War. While a knowledge of traumatic surgery is of value, more than that is needed for the practice of neurological surgery in civil life. However, we learned much from the experiences gained in the first World War.

For example, in high explosive and bullet wounds of the skull and spine, the method of *débridement*—the excision of lacerated soft and bony tissues—proved to be of great value for the prevention of secondary infection of the brain or spinal cord and their meninges. If the area in which infectious material has been implanted can be excised, the wound may often be closed with resultant primary union. The method of *débridement* was most useful in the treatment of wounds of the extremities and of the peripheral nerves. The conflict that is now raging will no doubt, as in the first World War, produce a large number of bullet and high explosive wounds of the upper and lower limbs. In his very recent report of experiences at Pearl Harbor, Dr. John Moorhead made special reference to the high frequency of wounds of the nerves of the extremities. During the first World War, the method of *débridement* and the use of chlorine solutions (Carrell-Dakin treatment) greatly diminished the frequency of wound infections. However, it may not be amiss to call attention to one danger of *débridement*. Having had occasion to operate upon a large number of soldiers with peripheral nerve injuries after they had been invalidated home from the battlefronts, I learned that occasionally evidence of complete interruption of the function of a large nerve followed only after the mass extirpation of lacerated soft tissues. In some of the cases, one was led to suspect that the neural lesion was produced by the surgeon. The functions of a large nerve may be preserved even though the nerve traverses an area that is infected or even an area of actual suppuration. Therefore, especially with the sulfathiazole treatment of wounds, every effort should be made by the surgeon to preserve nerves which have not been injured and those that are only traumatized, especially those nerves, such as the ulnar in the upper and the sciatic and its branches in the lower limbs, in which regeneration after nerve suture is poor.

It is to be hoped that the follow-up of patients in whom nerve transplants have to be used to bridge nerve defects will be better than that after the first World War. After the former conflict, there was not an efficient follow-up, and our knowledge is still meager regarding the final results in these individuals in whom the separated nerve ends could not be united by suture and transplants were used. In these patients, many types of operation were tried but we do not know which methods gave the best results.

Aside from these surgical matters, the neurologist learned much from

the experiences of the former conflict. Thus, the *coup-de-grace* was given to the so-called Bastian-Bruns law regarding the symptoms and signs of complete transverse lesions of the spinal cord. You will remember that for many years the symptoms of a complete transverse lesion of the spinal cord in man were supposed to consist of permanent loss not only of sensation and voluntary motor power below the level of the lesion but also of persisting absence of all tendon and cutaneous reflexes. We now know that after a certain period there is a return of spasticity and of reflexes without, of course, any return of sensation or voluntary power. The experiences of the first World War increased our knowledge of the location of functions in different parts of the brain and spinal cord, of mass reflexes and of automatic activity of the urinary bladder.

When one looks back upon neurological surgery as it was in the early days of the specialty and compares it with the work of today, the differences are great and impressive. At that time we had not learned that the "enacting clause" in operations for tumor of the brain was the diminishing of the increased intracranial pressure. Can you imagine the difficulties of the neurosurgeon before we learned of the value of hypertonic solutions and of the method of puncture and evacuation of fluid from the ventricles and subarachnoid cisterns in order to lessen intracranial tension? In those days the patients were always anesthetized—usually by ether which by itself raises intracranial pressure. We had to learn that these operations could and should be performed under local infiltration anesthesia—a method first recommended for cranial surgery by Dr. DeMartel of Paris. In this country, I believe, the first cranial operations for tumor of the brain under local anesthesia were performed by myself at the Neurological Institute of New York. As you know, local anesthesia is now used for the majority of cranial operations and it is especially effective when the patient has received avertin before he is brought to the operating room.

During the past decades, great advances have been made in the methods of hemostasis: First came silver clips, then the use of muscle, and finally the high frequency current. Many improvements were made in the methods of making bone flaps and in the technique of exposure of tumors on the under surface of the brain; of growths in the cerebellopontine angle and in the cerebral ventricles. The methods of excision of infiltrating tumors of the brain have become more and more

radical so that today no neurosurgeon would hesitate to excise the greater part of one cerebral or cerebellar lobe. It is very questionable, however, whether there is ever any justification for the total or subtotal removal of a cerebral hemisphere.

I have wandered somewhat afield and away from the story of the development of neurological surgery in New York City. During the past 25 years, New York City has had twenty-three surgeons who limited their work to the surgery of the nervous system. With the possible exception of two of these, all of the surgeons have had a training in neurology and neurosurgery, either in one of our local institutions or in a neurosurgical clinic in some other city. It may be of interest that we have had one woman specialist in this field. At the present time there are in the greater city of New York sixteen active neurological surgeons and several younger men who are beginning to devote themselves to the specialty.

During the first part of the 25 year period, there were neurosurgical departments at the Neurological Institute and at Bellevue and The Mount Sinai Hospitals. The service at the Neurological Institute was directed by me, and associated with me were Drs. Alfred S. Taylor, Byron Stookey, James H. Kenyon, Clement Masson, Wilder Penfield, Dorothy Klenke, Leo M. Davidoff, Edwin Deery, Fritz Cramer and Earl D. Brewer. When I retired from the ward service, Dr. Stookey was appointed to take charge, Dr. Davidoff resigned in order to become surgical director of a Brooklyn hospital, Dr. Deery resigned, and Dr. John Scarff was appointed a member of the surgical staff. Previous to this period, Dr. Penfield had resigned in order to become the Director of the Montreal Neurological Institute, Dr. Klenke had resigned and the Neurological Institute had lost Dr. Brewer and Dr. Kenyon through death. In 1938 Dr. Tracy J. Putnam was appointed chief of the neurological and neurosurgical services of the Neurological Institute.

At Bellevue Hospital the neurosurgical service was in charge of Dr. Taylor, and at various times there were associated with him Dr. Stookey and Dr. J. J. King. Later, the work at Bellevue was done by Dr. King, Dr. Scarff and lately by Dr. Lawrence Pool.

Up to 1927, the neurosurgical service at The Mount Sinai Hospital was in my charge and that of Dr. Ira Cohen; upon my resignation, Dr. Cohen became the head of the service with Dr. Kaplan and Dr. Sidney Gross as associates.

Although there was no special neurosurgical department at the Presbyterian Hospital, considerable work was done in that institution by Dr. Penfield and Dr. William Cone before they left for Montreal and the histological and pathological studies made by them in the laboratory for neurocytology organized by Dr. Penfield deserves special mention. At the Brooklyn Jewish Hospital, Dr. Davidoff a few years ago organized a neurosurgical service, and he has been doing a large amount of operative work in that institution. In Brooklyn, considerable neurosurgery has also been done in several hospitals by Dr. Jefferson Browder, and some by Dr. Anatole Kolodny.

Recently, an efficient department for the operative treatment of diseases of the nervous system is being developed by Dr. Bronson Ray at New York Hospital, and during the past two decades some operations on the nervous system have been done in other hospitals by neurosurgeons at St. Luke's Hospital and at the Post-Graduate and the Poly-clinic Hospitals and a few other institutions.

A certain number of operations for fractures of the skull and the spine were and are still being performed by general surgeons at various hospitals in our City, but the general tendency has been—whenever and wherever possible—for fractures of the skull and the vertebral column to be cared for by the neurological surgeon.

During the early years of the 25 year period, abscess of the brain complicating middle ear disease was cared for and operated on by the otologist. As the field of neurological surgery became more specialized, these patients were more often referred to the neurosurgeon and today most of these operations are performed by the surgeon who specializes in this field.

Finally, I may be permitted to give a short account of some of the contributions to neurology and neurosurgery made by the special workers in the latter field in our city:

A number of years ago, Dr. Alfred S. Taylor, who by the irony of fate recently succumbed to an infiltrating tumor of the brain, developed the technique of operations for birth injuries of the brachial plexus, and he also described the operation of unilateral laminectomy and devised ingenious instruments for that operation. Much of Dr. Taylor's work was done at Bellevue Hospital and at the Neurological Institute. Also, on the special service at Bellevue Hospital, Dr. J. J. King did important work on the methods of operation for abscess of the brain.

I have already referred to the valuable studies on the glia by means of the newer staining methods that were made by Dr. Penfield and Dr. Cone.

I think that it is fair to state that to the development of the surgery of the spinal cord, New York surgeons made important contributions. The technique of the operation of laminectomy was developed by them, and they added much to our knowledge of the clinical features and the diagnosis of tumors and other lesions of the spinal cord and its membranes. The clinical symptoms and surgical treatment of the so-called giant tumors of the conus and cauda equina—which are most often ependymomas—were first described by neurosurgeons of our city and the same is true of varicosities of the spinal blood vessels and of extradural cysts of the spinal cord.

The improvements in the methods for performing manometric tests for the determination of the presence or absence of spinal subarachnoid block were no insignificant contribution. The refinements in the methods for testing the patency of the spinal subarachnoid space were made by Dr. Stookey and his collaborators. To neurosurgeons of our city also belongs the credit for having devised the method for the exposure of the anterior surface of the spinal cord in order to remove tumors from in front of the spinal cord and to treat other lesions in that situation.

It was formerly believed that the malignant tumor of the brain, which is now called glioblastoma multiforme,* occurred most often in the frontal parts of the cerebral hemispheres and especially often on the left side. The study of a large number of cases at operation and postmortem convinced us that the growth is most frequently situated in the parietal lobe although it often extends forward to involve the frontal lobe and more especially the inferior part of the temporal and frontal lobe of the brain. With another investigator, one of us called attention to the fact that glioblastoma multiforme of the brain frequently runs a very rapid course—a course quite different from that of most cerebral growths. The history of the patient's illness may be of only one or a few weeks duration and the symptoms run an acute course.

Profound disturbances in motor power and sensation and advanced mental deterioration often come on very rapidly. For this reason, we

* For reasons that have been frequently expressed in print, I still believe that the term "pongioblastoma multiforme," originally given to the growth by Globus and Strauss, is preferable.

TABLE I

RESULTS OF OPERATIONS IN 83 PATIENTS WITH GLIOBLASTOMA MULTIFORME OF THE BRAIN

| | | | |
|---------------------------------|----|-------------|---------------|
| Death within 4 weeks..... | 44 | 53 per cent | } 84 per cent |
| “ “ 4 months | 10 | 12 per cent | |
| “ “ 1 year | 16 | 19 per cent | |
| “ “ 1-2 years or more | 9 | 11 per cent | |
| Living 4 months after operation | 1 | | |
| “ 8 “ “ “ | 1 | | |
| “ 10 “ “ “ | 1 | | |
| “ 22 “ “ “ | 1 | | |

suggested that these growths might be called “acute” brain tumors. I think that there is some doubt whether the glioblastoma multiforme is a true neoplasm or whether it is a tumor formation resulting from an intense glial reaction to some noxious agent. If this point of view should be shown to be correct, then it is clear that in the future the proper treatment of this type of tumor will rarely be surgical. The results of the operative treatment of glioblastoma multiforme are poor and relatively few patients survive for more than one year. This is shown, for example, by the results in the series of cases presented in Table I—results which about correspond to those obtained in other neurosurgical clinics.

Another type of tumor which we have studied is the midline posterior fossa medulloblastoma which occurs so often in childhood. Many attempts have been made radically to extirpate these growths, but they can rarely if ever be entirely removed because of their vascular attachment in the lower part of the fourth ventricle. This type of tumor is very radiosensitive, and we have shown that as good if not better results can be obtained if the effort is not made to remove the growth. In most instances, by a wide suboccipital decompression with removal of only sufficient tumor tissue for pathological verification, followed by thorough Roentgen-ray therapy, as much will be accomplished and relief will last as long as after the attempt to remove the growth entirely. Moreover, if one takes into account the higher operative mortality of an attempted radical operation, the total results of the operative treatment of the medulloblastoma in the posterior cranial fossa are better with conservative surgery and radical Roentgen therapy.

The early diagnosis of benign tumors underneath the frontal lobes of the brain—more especially the olfactory groove, cribriform plate and

sphenoid ridge meningioma—is important for their surgical treatment. When these growths have reached a large size, the difficulties and dangers of their removal are much increased, and in some instances the large growths can not be entirely removed. We, in New York City, have been greatly helped by a New York roentgenologist, Dr. Cornelius G. Dyke, and his studies of the basal arachnoid cisterns after the injection of air or oxygen by the lumbar route. With a neurological surgeon Dr. Dyke was able to demonstrate that many subfrontal meningiomas, especially those which originate from the dura over the mesial end of the sphenoid ridge, can be recognized and be removed when they are still small—weighing only a few grams.

That the diagnosis of some tumors of the spinal cord can be made by careful measurements, on Roentgen films of the spine, of the distances between the pedicles, was demonstrated by the same roentgenologist with a New York neurosurgeon. Studies of a large number of Roentgen films of the spine were correlated with the operative findings and we learned that certain spinal growths regularly produce a localized enlargement of the spinal canal which can be recognized when the interpediculate distances are carefully measured. By these measurements it was possible to demonstrate that the spinal meningiomas rarely, and the spinal perineurial fibroblastomas frequently, cause localized enlargements of the interpediculate distances. An enlargement of the vertebral canal extending over several vertebrae is characteristic of the extradural cysts and of the so-called giant tumors of the conus and cauda equina.

The clinical picture of high cervical spinal cord tumors which project through the foramen magnum was first described by a New York surgeon and a neurologist. Attention was called to the fact that in operations for these growths it is always necessary and advisable partly to expose the structures in the posterior cranial fossa by the removal of some of the occipital bone. If this is not done, a part of the growth above the level of the foramen magnum may be missed altogether—an unfortunate occurrence which happened in our first case and which taught us a valuable lesson.

Finally, one may ask: what of the future? That old Roman, Cicero, said that “in no function do human beings approximate the Gods more closely than in bestowing health upon their fellowmen.” We must change methods or improve them as soon as we learn that we are using a procedure by which little or nothing is being accomplished. There

are some diseases of the nervous system for which surgery has been able to do little or only to palliate, and for these, new surgical methods must be sought for or the treatment must not be surgical. Thus, it is probable that when the diagnosis can be made—and it can be made in many instances—fewer operations will be done in the future for the malignant glioblastoma multiforme. Future therapy may be radiological or perhaps serological. In purulent infection of the meninges the therapy of the future may not be surgical. The isolation and synthesis of many of the vitamins by the biochemists have opened up a large field for clinical investigation and “these discoveries of the biochemists, if applied to the prevention and treatment of diseases of the nervous system, may be compared in importance to the discoveries in bacteriology made 40 to 50 years ago.” Is it too optimistic to expect that some diseases of the nervous system which produce great disability, such as spasticity and tonic and clonic seizures, and for which surgical procedures are being attempted, will in the future be prevented or treated by medical means? This does not mean that neurological surgery will not continue to advance. We can not expect that the progress in operative methods and technique in the next twenty-five years will be as great as that made in the same period that has passed. The further progress of neurological surgery will be more slow, but new procedures and greater refinements of technique are certain to come.

WHAT EVERY PHYSICIAN SHOULD KNOW ABOUT CROSS-EXAMINATION

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PHYSICIANS are in court almost as frequently as lawyers. It is said that court records in New York City would reveal that suits involving personal injuries constitute about 70 per cent of the litigation. Since each side will have at least one physician, there are at least as many doctors as lawyers in every such case. This situation is not peculiar to New York City; it is reported that it exists throughout the United States. Furthermore, personal injury actions are not the only species of litigation where physicians are required. Doctors testify in goodly numbers in will contests involving insanity, in various criminal trials, such as assault, rape, homicide and the like, and in health, accident and disability insurance cases. All in all, it appears that the physician is quite a "man about court." Wisdom would appear to dictate that physicians should familiarize themselves with the problems of witnesses.

A famous English barrister once said, "There is never a cause contested, the result of which is not mainly dependent upon the skill with which the advocate conducts the cross examination." This statement was made in the days when flowery oratory was in vogue and when it played a very important part in the trial of cases. Today, that form of oratory is passé, and it plays a minor role in litigation. If cross-examination was the decisive factor in litigation in those days, it is doubly true today. Though the quotation set forth here was made to convince lawyers to become proficient in the art of cross-examination, it is equally appropriate for witnesses. This is especially so for physicians because more is expected from the professional expert by the triers of the facts. Any person who takes the stand will make a better and more convincing witness if he becomes familiar with the methods utilized by cross-examiners.

All witnesses are subjected to both direct-examination and cross-examination. Both terms should be defined and explained simultaneously

if the process of cross-examination is to be fully appreciated.

Law dictionaries define direct-examination as the examination of a witness by a lawyer who calls the witness to the stand and who first examines him, and they define cross-examination as the examination of such witness by the adverse lawyer, after the conclusion of the direct examination. Webster's Collegiate Dictionary defines "Cross-Examination" thus: "To examine or question, especially as a check to a previous examination."

The true significance of cross-examination and the purpose and utility of the process and the reasons for its effectiveness can be fully appreciated and understood only if it is examined in the setting in which it is used and of which it is an integral feature—the trial of a case in court. Cross-examination is a practical art and it is natural that it fitted and adapted itself to its setting.

The principal feature of this setting, in so far as cross-examination is concerned, is that the direct examiner presents only such evidence, and calls only such witnesses, and asks only such questions as will favor the side of the examining lawyer. The direct examiner will ask for nothing except facts favorable to his own side. The direct examiner does not ask the witness to disclose all that he knows, and the witness does not do so. If the examination of the witness stopped at this point and no attempt was made to find out what else he knows, the testimony would probably present half truths only. The direct examiner does not ask questions that might impair or discredit the story or the witness that he presents to the judge and jury. The factors that might weaken the original testimony or that might lessen the credit of the witness might remain hidden if the examination were to end there. The best person to make the search for what remains hidden, the undisclosed remainder, is the person who is most interested, the opponent. Thus, when the direct examination is concluded the cross-examiner is given an opportunity to complete the picture—to develop and bring to light those facts and circumstances which may have been suppressed on the direct examination. If any facts unfavorable to the direct examiner's case really exist and these are to be learned, the cross-examiner must ferret them out.

The practical effect of all this is that the cross-examiner will probe only for such facts as will be unfavorable to the direct-examiner's case. Since partisan counsel will, between them, endeavor to bring forth all

the favorable and unfavorable facts concerning each side, a fair appraisal of the witness and the stories should ultimately result.

Whenever partisans present evidence, it is desirable, before any evidence is accepted as wholly trustworthy, that it be subjected to testing and checking. The test can be effected by subjecting the offered evidence to a scrutiny and analysis calculated to discover and expose, in detail, its possible weaknesses and thus to enable it to be estimated at no more than its actual value. That is the function of a cross-examination and it is called the finest weapon ever invented to discover truth.

The ultimate objective of a cross-examination is to extract from the witnesses whatever may be unfavorable to the direct examiner's case. The unfavorable matter would be of two varieties, (1) facts that support the cross-examiner's contentions, and (2) facts that discredit the witness or the story or that weaken the direct examiner's case.

To extract each unfavorable fact constitutes a separate and distinct objective for the cross-examiner in every case. The nature and character of the unfavorable facts will vary with the case and the witness. The number of possible unfavorable facts is limitless.

An illustration will serve to clarify and explain this statement: A case of assault will be assumed. The sole disputed issue is, "Did defendant shoot plaintiff at 3 A.M. on November 30, 1939 in Grand Central Station?" The plaintiff contends that the defendant did this, and the defendant denies it. Though a single issue exists, it contains three elements: (a) did the defendant shoot the plaintiff, (b) did the shooting occur at the Grand Central Station and (c) did it occur at the time in question. Separate witnesses may be called to prove each element of, or the whole of, this proposition. Witness Roe is called by plaintiff and says that plaintiff and defendant were at Grand Central Station immediately before 3 A.M. on November 30, 1939. The witness is then turned over to the cross-examiner for questioning. The cross-examiner will ask himself: "What facts can be extracted from witness Roe that will be unfavorable to the plaintiff's case?" A very meager list of facts that would tend to support the defendant's proposition, or that would tend to discredit witness Roe, or the statement that plaintiff and defendant were at Grand Central Station at the time specified are these: Roe did not actually see the plaintiff and defendant at the Grand Central Station at the time in question, he simply heard they were there from plaintiff, Roe is a confirmed liar, Roe would not recognize the

plaintiff or the defendant if he saw them, his eyesight is very poor, Roe is related to and very friendly with the plaintiff, it was very dark at the time and place in question and Roe could not have seen these men, plaintiff and defendant were very friendly both before and after this occurrence, defendant did not own a weapon, Roe was convicted of numerous crimes including perjury, Roe is very susceptible to suggestion, Roe's statement is improbable in numerous particulars, he had innumerable talks about the matter with plaintiff and his lawyer, that Roe made previous contradictory statements and that he is biased and prejudiced against people like the defendant.

Any or all of these facts would tend to create doubt or disbelief in the proposition being maintained by the plaintiff. The list of unfavorable facts set forth here could be expanded almost ad infinitum.

This illustration should make the distinction between the two varieties of unfavorable facts more apparent. Facts of variety number one (those that support the cross-examiner's contentions) are not intended to impugn or impeach the credit or trustworthiness of the story or the witness. Factual examples of variety number one in this suppositious case are: the plaintiff and defendant were very friendly before and after the time when the shooting is supposed to have occurred and that the defendant never owned a weapon. These two facts do not impeach Roe's trustworthiness or contradict Roe's statement that plaintiff and defendant were at the Grand Central Station at the time specified. These two facts merely lend support to the cross-examiner's contention that the shooting did not occur, on the theory that it is improbable that the defendant shot plaintiff if they were so friendly both before and after the occurrence was supposed to have taken place, and if the defendant never owned a weapon. The search for facts of the second variety is made to induce disbelief, or to destroy confidence or trust in the story or the witness or both.

The art and the skill in conducting an actual cross-examination consists in knowing when to question a witness and in knowing what to extract from each witness and how to do it.

To cross-examine or not to cross-examine, that is the first question. Cross-examination is a double edged sword. It is a dangerous weapon to use. Before a lawyer commences to question each witness, he wonders, "What hidden facts will the cross-examination reveal? Will these hidden facts strengthen or weaken the case of the cross-examiner?"

Will they show that the witness is trustworthy or unreliable? Will the cross-examiner develop facts favorable or unfavorable to the cross-examiner's case? Will the answer give the witness a personal victory over the cross-examiner?" The lawyer faces this dilemma before every question is asked on cross-examination unless he knows in advance exactly what answer the witness will give in response to each question. What an enigma for the cross-examiner who is in doubt as to what the witness may know or say or do. "There lies the real danger in cross-examination and there begins the art."

The danger is enhanced by the fact that if a witness is strenuously cross-examined and not impeached in any particular, the story and the witness will be strengthened in the eyes of the triers of the facts, on the assumption, that a witness who is not discredited after a thorough and searching cross-examination must be telling the whole and entire truth. Though the belief is common among witnesses and juries that "a lawyer can do anything with a cross-examination," that he "may make the worse appear the better reason" and that he "may make the truth appear like falsehood," lawyers know that these ideas are wholly without basis or foundation. Cross-examination has been aptly described as a "mental duel" between lawyer and witness. This "duel" often results disastrously for the lawyer as these illustrations reveal:

An instance is furnished by a surgeon's suit for a substantial fee. "Can you tell me," asked the lawyer, "How long it took to knock off that operation?" "Two hours" replied the surgeon. "The labor of two hours then is that for which you ask \$1500?" "No," replied the surgeon, "I ask it for the knowledge of a lifetime." The lawyer asked one question too many in this exchange with a renowned surgeon, and came off second best.

A well known illustration, reported by Wigmore, concerns the famous Lord Coleridge in the case involving a Sister of Mercy, who was expelled for transgression of the rules of the Convent, and therefore commenced suit for libel. Coleridge contended that the breaches of discipline were trivial. He pressed Mrs. Kennedy, "the matron," on the point, asking what had Mrs. Saurin done? Mrs. Kennedy said as an example that she had eaten strawberries. "Eating strawberries!" exclaimed Coleridge, "What harm was there in that?" "It was forbidden, sir" said Mrs. Kennedy—a very proper answer. "But Mrs. Kennedy" reiterated Coleridge "what trouble was likely to come from eating

strawberries?" "Well, sir," replied Mrs. Kennedy, "You might ask what trouble was likely to come from eating apples, yet we know that trouble did come from it." The answer floored Coleridge.

Though art of cross-examination begins with knowing when "to cross-examine or not to cross-examine," it centers around knowing what to extract from each witness so that the direct examiner's case may be weakened, and his witnesses and their testimony discredited, and in knowing how to extract it. So that physicians may more successfully cope with an effective cross-examination, the methods employed by cross-examiners to achieve these ends are for convenience and simplicity being arbitrarily divided into four categories: (1) The vulnerable points of the case; (2) Material for cross-examination; (3) Fixed objectives and (4) The manner of questioning the witnesses.

1. The cross-examiner constantly hunts for the vulnerable spots in the story and the witness—those vital spots that seem most susceptible to a successful attack. The skillful cross-examiner develops a sixth sense in discovering the vulnerable points in each case. The vulnerable points in a given case may be its most improbable feature or a particular trait or characteristic of a witness. The facts in each case, and the make-up of each witness, determine the points of vulnerability in the matter. The physician's records, or the fees said to have been received, or the nature of the treatments administered may reveal angles that will serve as targets for investigation. Similarly, features affecting the witness himself may lead to the place where the attack should be directed—examples of these would be: The witness's memory or his opportunity to observe what he claims he saw or the witness's temper or stubbornness or bias or relationship to a litigant. There is really no limit to the possible number of vulnerable spots that can be selected.

2. While the direct examination unfolds, and while the cross-examination is in progress, the cross-examiner searches for material for cross-examination—the ammunition that the cross-examiner uses for attacking the witness. Whereas the vulnerable spot is the target, the material for the cross-examination is the weapon with which the attack is made. The finest ammunition is a statement, or a writing, that contradicts or is inconsistent with a witness's oral testimony. The search for material really commences long before the trial. The search is made for everything and anything that might

affect the witness's credit or contentions.

3. An effective cross-examination demands that counsel have definite and fixed objectives in mind while the cross-examination is in progress. However, wherever possible, the cross-examiner keeps these objectives hidden from the witness. It is axiomatic that "the only way to get anywhere is to know where you are going." This is especially appropriate advice for cross-examination. These fixed objectives may be broad or narrow. To discredit a witness or a story may be the mission of the cross-examination or it might consist in being to secure an admission from the witness that he "does not remember what happened on November 30, 1939 at 3 A.M. at Grand Central Station." Each unfavorable fact that counsel might elect to extract can constitute a separate fixed objective for the cross-examiner. To explore generally into a particular subject matter could likewise be an objective. Any end might serve as an objective for the cross-examiner.

4. It is the answer rather than the question that weakens the case or impeaches a witness. It is the answer that either affirms or denies the unfavorable facts that the cross-examiner seeks to extract. The cross-examiner's problem is to persuade the witness to give or to obtain from him the desired answer. The questions are simply the means by which these objectives are attained. Since witnesses do not always easily or willingly disclose the answer that is wanted, a plan of attack (a method of questioning each witness) will be devised that is best calculated to achieve the desired end. The technique of questioning witnesses actually utilized in law courts is based on sound and tested principles of logic, psychology and human nature.

The method of questioning witnesses naturally varies a great deal. The cross-examiner sometimes adopts a rapid fire method of questioning. This is tried to prevent a witness from manufacturing a story as the examination proceeds. The rapidity of questions may force the witness to answer truthfully because he is not given time to create a cohesive fabrication. The psychology of suggestion is another device of the cross-examiner. Here the form of the question is intended to suggest an answer. With a pliable witness, the question may be phrased so as to suggest the desired answer. With a hostile or stubborn witness the question may be so phrased that

the desired answer is wholly contradictory to what the witness thinks the cross-examiner wants. Being a contrary-minded person, or an individual who does not want to be led, this witness will disagree with what he thinks the cross-examiner wants—irrespective of whether it is true—on the theory that an answer opposite from what the cross-examiner apparently seeks must be good for the side this witness favors. What may be called the “off-guard technique” is often used with success. There a witness will be asked a series of questions on an apparently immaterial problem, and then a pertinent question will be shot at the witness on the subject about which the cross-examiner is most anxious for information. The witness may be off guard and thus give a truthful reply. With a malingering faker claiming deafness, the cross-examiner may ask the witness as he leaves the stand—when the witness is less alert, believing that the examination is concluded and in a voice too low to be heard by the witness if his claim of defective hearing were true—“Mr. Jones, didn’t you forget this piece of paper?” If the witness hears the question, he will probably give an answer. It must be apparent that illustrations of this character could be set forth without limit. Those given are merely intended to give the reader a sketchy idea as to what is meant by the “ways of questioning” a witness.

Though each witness and each case is an individual problem for the cross-examiner, for decades similarities were discerned by experienced cross-examiners both in witnesses and in the factual situations as to which witnesses were questioned. Experience taught the trial lawyer that with witnesses of a similar kind, or with a like factual situation, a reasonably effective cross-examination could be conducted along substantially similar lines. Substantially identical cross-examinations—here called standard patterns of cross-examination—thus developed, and these standard patterns were passed down by lawyers from generation to generation. So long as they worked satisfactorily they were used. When “existing” patterns cease to be effective, lawyers will develop new ones. Where similar witnesses or factual situations occur frequently, the cross-examination for that character of witness or situation becomes quite standardized and routine. The lawyers themselves do not always realize when a given examination is a “standard pattern of cross-examination.” Unfortunately and all too frequently, the cross-examiner’s “stock in trade” consists of a few “standard patterns” and when these are ex-

hausted without advantage to the cross-examiner, the lawyer feels more beaten than the witness.

Based on these similarities, witnesses and factual situations are classified, typed and catalogued for cross-examination. There are various types and kinds of witnesses, the exaggerator, the child and the expert and the like. Substantial similarities will exist for each of these separate types. The variety of different factual situations is equally numerous. There would be included here the automobile accident, the execution of a will, the making of a contract and any kind of factual situation involved in litigation. Each of these factual situations will have certain things in common. Nothing appearing here is intended to convey the impression that standard patterns of cross-examination are tricks. They are nothing of the kind. The "standard patterns" are sound legitimate methods of cross-examination based on tried and tested principles. No case is ever concluded without some examples of standard patterns of cross-examination. This article will consider those patterns of cross-examination that will confront the physician most frequently.

"Never cross-examine an expert in his own field" is an oft repeated adage. This advice is earnestly followed by skillful lawyers in the examination of physicians. Lawyers thus avoid a cross-examination of the purely medical aspects of the physician's testimony, unless the character of the litigation makes it essential for the lawyer to study and acquaint himself thoroughly with such phases of the case. Physicians must anticipate, therefore, that generally, they will be cross-examined concerning non-medical matters.

Before illustrating standard patterns of cross-examination with typical appropriate examples, a word of general advice to witnesses with respect to the art of answering questions might be in order. Though this advice may appear too obvious, it is amazing how infrequently it is followed. The witness should listen to each and every question carefully and he should think over the question before hazarding an answer. The witness may and should take all the time that may be reasonably necessary to give an answer. No extra points are scored for speed. If the witness does not understand a question he should say so and request that it be repeated. If the meaning of the words are not clear, he should ask for enlightenment. It is better to be known as an *ignoramus* than a liar. If the witness does not know, or remember the answer, he should say so. If he is not sure or certain of the answer, he should reply that

he believes, or thinks, that the correct answer is so and so, but that he is not sure or certain of it. However, the solution for this, is not for the witness to answer that he does not know or does not remember when he does in fact know, or does in fact remember, for this is a false answer. If a witness was asked, "Did you ever serve a term in Sing Sing prison," the answer "I do not remember" would hardly satisfy.

The witness should answer the specific question asked. This may seem like unnecessary advice but it really is quite important. Each answer should be responsive to the question. If the witness gives an unresponsive answer the jury may believe that he is deliberately attempting to be evasive. Volunteering information not called for may be quite dangerous, and it may serve to give the cross-examiner ammunition to discredit the witness. Many famous cases illustrate how the habit of answering only the question asked, and of avoiding the practice of volunteering information not called for in the question proved extremely helpful to the side that called the witness. A classic illustration of this principle is reported by Reed on "Conduct of Law Suits":

"Some time ago the writer, while waiting in court, watched the trial of a case where the plaintiff sought to recover damages for a breach of warranty. The defendant had sold him a horse with an express warranty that he was sound and kind and free from all 'outs.' The next day the plaintiff noticed that a shoe was loose, and he undertook to drive him into a blacksmith's shop to have him shod, when the horse exhibited such violent reluctance that he was obliged to abandon the attempt. Repeated efforts made it evident that he never would be shod willingly, and therefore he was obliged to sell him. The defendant called two witnesses. The first, an honest, clean looking man, testified that he was a blacksmith, that he knew the horse in question perfectly well, and he had shod him about the time referred to in the plaintiff's testimony. 'Did you have any difficulty in shoeing him?' asked the defendant's counsel. 'Not the least. He stood perfectly quiet. Never had a horse stand quieter.' The other, a venerable-looking man, with a clear, blue eye, testified that he had owned the horse and that he was perfectly kind. 'Did you ever have any trouble about getting him into a blacksmith's shop?' 'Well, sir, I don't remember that I ever had occasion to carry him to a blacksmith's shop while I owned him.'

"The plaintiff's counsel evidently thought that the cross-examin-

ation would only develop this unpleasant testimony more strongly, so he let the witnesses go. The jury found for the defendant. The next morning, as the writer was sitting in court waiting for a verdict, a man behind him, whom he recognized as the blacksmith, leaned forward and said, 'You heard that horse case tried yesterday, didn't you? Well, that fellow who tried the case for the plaintiff didn't know how to cross-examine worth a cent. I told him that the horse stood perfectly quiet while I shod him; and so he did. I didn't tell him that I had to hold him by the nose with a pair of pincers to make him stand. The old man said he never took him to a blacksmith's shop while he had him. No more he did. He had to take him out into an open lot and cast him before he could shoe him.'"

Witnesses should remember that it is not essential to impress the jury that they possess a high I.Q. They should convey the impression that they are honest, fair and trustworthy. This is especially so where the witness is being asked to testify as to facts. Where the witness is called upon to express an opinion, or to act as an expert, the learning, the qualifications and the experience of the witness then become quite relevant.

A few examples of "standard patterns" of cross-examination follow:

1. An investigation as to a physician's qualifications and experience is a "standard pattern" of inquiry. The investigation will ordinarily cover the physician's hospital connections, the phases of medicine in which he specializes, the number of cases similar to the case in suit that he has previously handled, his experience in the field of medicine under inquiry, his familiarity with the medical writings on the subject and all those factors from which a doctor's qualifications and experience are usually measured. The physician's answers should be frank and fair and his qualifications should not be exaggerated or minimized. The witness stand is not the place for self-praise or self-derogation. Each can be ruinous for the physician. An example of what happened to a physician who tried to appear more learned than he actually was is set forth at this point. It involved a suit for disability insurance benefits. Plaintiff claimed total disability as a result of a heart condition—angina pectoris. The insurance company's physician was a heart specialist. Counsel for the plaintiff came to the conclusion that the defendant's physician was inclined to exaggerate; that he was unwilling to admit ignorance on any subject affecting heart disorders. The witness gave the impression of being an unusually pompous individual. Plaintiff's counsel thereupon

prepared a list of texts which included two fictitious works. "Harrison on Heart Disease" and "Page on Heart Failure," which were "manufactured" by counsel. The pertinent cross-examination relative to the medical authorities follows:

- Q. Are you familiar with the authoritative texts on heart disease?
A. Of course.
Q. I suppose that you have read the authoritative texts and refer to them constantly in your work, correct?
A. I would say that I possess most of them in my own library.
Q. Have you heard of Lewis on Diseases of the Heart?
A. Certainly.
Q. Have you heard of Levine on Clinical Heart Disease?
A. Of course.
Q. These books are standard authorities on the heart?
A. That is correct.
Q. I suppose that there are few books on the heart that are not known to you?
A. I would say that is correct.
Q. Have you heard of P. D. White on Heart Disease and Harrison on Heart Disease?
A. I have.
Q. What about Page on Heart Failure and Anderson on Heart Diseases?
A. Certainly.
Q. Would you say that you have read or examined all the books that I have mentioned?
A. I would say that I not only read them but studied them carefully as well.
Q. Do you know whether any of the books that I have mentioned contain statements contrary to the conclusions that you have made?
A. I do not recall, though I doubt it. If they exist, show the passages to me. You apparently have a number of medical text books on the counsel table.
Q. Do you keep abreast of all current writings on the heart?
A. That's essential in my specialty.
Q. How frequently would you say that you have had occasion to study or refer to the texts that I have mentioned?

A. I refer to them constantly in my practice.

Q. How recently have you done this with respect to the six texts that I have mentioned?

A. My practice compels me to do this constantly, it deals exclusively with the heart.

Q. How many standard texts on the heart do you find it necessary to refer to constantly?

A. That is a foolish question. I refer to the standard texts that you mentioned.

Q. Doctor, I show you this catalogue of medical books and ask you if it is not a fact that Harrison on Heart Disease and Page on Heart Failure, which you stated are standard texts, and which you constantly refer to and study in the course of your practice, are not fictitious and non-existent?

A. No answer.

This physician's trustworthiness and credit were certainly impaired. The impeachment of this witness could have resulted from a conscious design to deceive or from wholly innocent causes. All people, to a degree, are susceptible to the power of suggestion. All persons have had the experience, while conversing with a friend, of being asked "Why you remember David Dantos from back home" and they reply "Oh, of course," or "I think I do," when they don't recall the fellow at all. The witness stand is not the place to be accommodating or careless. It is during cross-examination that the witness must be especially alert and awake and scrutinize and consider each question before answering.

Courts and juries do not expect experts to know everything, and it is unwise for physicians to attempt to give this impression. No person need feel disgraced if he is compelled to say "I do not know," or "I do not remember."

2. A cross-examination concerning doctors' medical records is a very common subject of inquiry. An example of such an examination follows:

Q. Doctor, will you please let me see the medical records to which you referred on direct examination?

A. Shall I, Judge?

Court: Yes, doctor, since you used the records on direct examination, counsel has a right to examine them.

The physician hands the records to counsel who then proceeds to

examine them. The cross-examiner hunts for vulnerable spots in the records and searches them for material for cross-examination.

Q. Did you ever know or see this patient or treat him before this case?

A. Never before.

Q. Are these records in your handwriting?

A. Yes, they are.

Q. Now, doctor, weren't these records written up recently and all at one time?

A. Yes, they were. You are 100 per cent correct there. I wrote them up yesterday. I made this copy from my original records because of this court case.

Q. In what respect do your original records differ from or contradict these records?

A. They are identical.

Q. Are they on the same form of card?

A. Exactly the same.

Q. Have you the original records with you?

A. No, I didn't think I needed them and thus did not bring them with me.

Q. Where are the original records now?

A. At my office.

Q. And where is that?

A. Park Avenue, Manhattan.

Q. Why did you bring the copy with you instead of the original?

A. They are both identical. I felt it would suffice.

Q. It is now 2:30 P.M.—how long would it take you to get the original records and return with them.

A. I haven't got the time to do that.

Q. If my clerk should leave with you now, would it be possible for you to return to your office and give my clerk these original records?

A. I can't waste all day on this case.

Counsel: I ask your Honor to direct Dr. to pick up his original records and to return with them to court this afternoon.

(Colloquy between counsel and the court).

Court: Doctor, since the request for your original records

is made, I must ask you to get them and produce them. You will be excused for this purpose.

Witness: Frankly, your Honor, I do not think I could find them. I made these records yesterday intending to bring the original records to court, to leave the original records with the court if it desired them and to retain the copy as my permanent record. I placed the copy in my metal index file and put the original in my wallet pocket. This morning, I looked for the original records and could not find them. I searched for a half hour without success. They must be in my office or at home, somewhere. I suppose I should have admitted this before. I have never lost records before and felt quite embarrassed about it. I should not have tried to bluff my way out of it.

Q. When you tried to bluff your way out of it you knew you were under oath?

A. Yes, I did.

Q. When you stated that you did not bring the original records with you because you did not think you needed them, that was false and untrue, wasn't it, doctor?

A. Well, I suppose it wasn't true but I did feel that the copy would satisfy you.

Q. You originally intended to bring the original to court?

A. Yes, I did.

Q. So you testified falsely when you stated that you did not bring the original record because you did not think you would need it, is that not correct?

A. My answer was untrue.

When a witness takes the stand he swears that he will tell the truth, the whole truth and nothing but the truth. The cross-examiner hopes to catch the witness in a lie on the theory that if the witness lies in one respect the court and jury will believe that he is careless about the truth and that he is the lying kind. Bluff is not recommended. Physicians should always bring their original records to court. To produce copies will only create the impression that the originals are non-existent. This advice should be followed even if the copy is in a more convenient form. If the doctor desires to produce both original and copy, and leave the copy, should the court require it, this can be done. It is a mistake to leave the original at the doctor's home, or office.

A cross-examination as to a physician's records is so frequent an inquiry that a second example is being given. An effective cross-examination in this field is illustrated by a case involving a possibly fractured skull. The physician testified to these injuries: a deep laceration on the hand, a period of unconsciousness (ten minutes), bleeding from the nose and ears, nausea and headache. These are what the physician found on the first visit. X-rays of the skull were taken in various positions. The pictures were negative. The doctor's diagnosis was a fractured skull. The doctor kept the patient in bed for three weeks.

After the doctor's records were turned over to counsel, the cross-examination proceeded in this manner:

Q. Notwithstandnig the x-ray you persist in your diagnosis of a fractured skull?

A. Yes, a fracture of the base of the skull. The x-ray is not conclusive. To me the findings are more impressive.

Q. Without what signs and conditions would you not have made a diagnosis of fractured skull?

A. All the things I found are important. I am not sure that I quite follow you.

Q. If the plaintiff had not suffered from headaches and nausea when you first examined him, would you have made a diagnosis of fractured skull?

A. He was suffering from these and told me so.

Q. I repeat, if you did not find the plaintiff suffering from headache and nausea, you would not have made that diagnosis, is that correct?

A. Without nausea, I still may have, in view of the other findings, without head pains, no.

Q. Without bleeding from the nose and ears, would you have made that diagnosis?

A. Without bleeding from the nose, yes. Without bleeding from the ears, no.

Q. If there was no bleeding from the ears you could not have made a diagnosis of fractured skull in this case.

A. That is absolutely correct.

A series of questions were then asked the doctor to divert his attention from the subject of bleeding from the ears.

Q. Have you an independent recollection of what you saw the

- plaintiff suffering from and what he told you, or is this case just like a thousand others and do you only remember what the patient had because of your records?

A. I remember this case very well.

Q. Do you remember asking your patient questions and summarizing on this card what you were told and what you found?

A. I put down what was important.

Q. You remember doing that in this case?

A. Yes.

Counsel now picks up the card, and while looking at it, asks these questions:

Q. You were told that the injuries resulted from falling plaster and you made a record as to that, correct?

A. Correct.

Q. Falling plaster could have caused a bloody nose?

A. There was no mark on the nose.

Q. You do not say there was no mark on the nose in this record, doctor?

A. Where there is no mark or injury to a part, I make no record as to that. I made no entry that there were no marks or injuries to the man's legs or toes, either.

Q. Since you knew this injury would result in a lawsuit, you were especially careful in the making of records, were you not?

A. I was primarily concerned with curing the patient, not winning a lawsuit.

Q. You knew there might be a lawsuit?

A. I did not think about it.

Q. You made a record of how the injuries occurred and all the injuries that you found and observed?

A. I always do that, accident or no accident.

Q. And you did that in this case?

A. I did.

Counsel continues to examine card as he questions the witness.

Q. You were told about headaches and you put that down?

A. Correct.

Q. Plaintiff told you about nausea and you put that down?

A. That's right.

Q. You saw a deep laceration on the skull and you recorded that

on this card?

A. I put down everything I saw that was important.

Q. You saw bleeding from the ears and you made a note as to that on this card?

A. I did.

Q. Doctor, you have an independent recollection of writing down all these things?

A. Of course.

Q. Do you recall whether you wrote the entry regarding the bleeding from the ears, with pen or pencil?

A. Pen.

Q. With what color ink?

A. I always use green ink.

Q. Your memory as to all this is clear enough so that you can see yourself doing all this?

A. Of course.

Q. And what plaintiff didn't suffer from you did not write down?

A. I have told you this before.

Q. Doctor, isn't it a fact that there is no entry whatsoever on this card regarding bleeding from the ears?

A. No answer.

The physician's records serve as a very fruitful beginning for a successful cross-examination. A written record is more eloquent and convincing than a thousand spoken words. The solution for a cross-examination as to records is more careful and thorough records, and a searching scrutiny of these records by doctor and counsel before the doctor takes the stand. There is no excuse for a physician being surprised as to the contents of his own records.

3. Physicians should anticipate a cross-examination as to hypothetical questions covered during the direct examination. In almost every case wherein a physician testifies, a hypothetical question is asked. Bouvier's Law Dictionary defines a hypothetical question as "a question put to an expert witness containing a recital of facts assumed to have been proved, or proof of which is offered in the case and requiring the opinion of the witness thereon." The standard pattern of cross-examination, with reference to such question is to proceed in either of two ways (1) to induce the expert to admit that a few specific facts among the many assumed facts in the question are the "sine qua non" or essen-

tial facts of the opinion without which the conclusion would not be possible, and then to attack the existence or non-existence of those essential facts, and (2) to ascertain how the opinion of the expert would be affected by adding to the hypothetical question new facts not originally contained in the question.

As an example a case is set forth here wherein the physician claimed that on an assumed state of facts it was his opinion that the decedent was insane. The assumed facts were as follows: decedent suffered from periods of excitement and depression; he refused to see four of his five children; he believed in spiritualism; he felt that four of his children were extremely anxious for him to die; he was very irritable and obstinate; he complained of constant headaches and these existed for about three years prior to the time decedent died, at the age of sixty-nine years; and he suffered from frequent and violent spells of intoxication and fits of temper. A few of the questions asked the expert follow:

Q. Would you say that everybody who believed in spiritualism was insane?

A. No.

Q. Would you say that a belief in spiritualism in and of itself is an evidence of insanity?

A. Not in and of itself, but I think it is an evidence of insanity in this case.

Q. Was the decedent's belief in spiritualism peculiar or different from the ordinary variety of spiritualism, and if so, describe in what way it differed?

A. I know of no way in which decedent's belief differed from general beliefs on the subject.

Q. Then is it correct that it is the decedent's belief plus the other facts assumed by you that convinced you that decedent's belief in spiritualism is important?

A. Yes.

Q. We agree, therefore, do we not, that a belief in spiritualism in and of itself is no evidence of insanity?

A. I would agree with you there.

Q. And the decedent's belief in spiritualism alone and in and of itself is no evidence of insanity, is that correct?

A. I would say so.

The same series of questions were then directed to all the assumed

facts in the hypothetical question. Counsel finally persuaded the expert to admit that three facts were sufficient by themselves to convince the doctor that decedent was insane, to wit, the fact that decedent believed that four of his children were anxious to have him die, that he refused to see four of his children, and that he suffered from periods of excitement and depression. The examination then proceeded in this way:

Q. Would you say that each of these three factors independently suffice to justify a conclusion decedent was insane, or would you say that the combination of these three factors compel that conclusion?

A. The combination.

Q. So that if any of these three factors did not exist you would say that there was an insufficient basis to form an opinion that the decedent was not sane?

A. Excepting if the decedent had practically continuous periods of excitement and depression without let-ups and without any periods of normalcy I might say that that alone was sufficient.

Q. However, you know that the hypothetical question did not assume any such state of facts?

A. Yes, that is true.

Q. And you know that there is no claim that the decedent suffered from practically continuous periods of excitement and depression and that the testimony is to the contrary, do you not?

A. Yes, so I have been told.

Q. So it is correct, is it not, that you believe that it is a combination of these three factors that brings you to the conclusion?

A. I suppose so.

Q. And that if any of these three factors did not exist you personally would not or could not come to the conclusion that decedent was insane?

A. I think that is so.

Q. If you should assume that before decedent refused to see four of his children, those children constantly demanded of decedent whenever they were with him that he divide his wealth among his children before he died, and whenever he would see these four children there were constant arguments and bickering concerning that subject with a result that decedent would become terribly ill and excited—would you say that his refusal to see

those four children was without cause or reason?

A. That would depend on just how violent the arguments and the bickering were.

Q. You do not consider it an evidence of insanity do you, if a man of sixty-eight years of age refuses to divide his wealth among his children, do you?

A. No.

Q. If four of decedent's children constantly harped on the subject, do you believe that a sane man might become aggravated and would find it unpleasant to see his children?

A. Those facts were not asked me when I rendered my opinion.

Q. Well, I ask you to assume those facts and ask you whether or not that would alter your opinion?

A. I would say that it probably would.

Q. If the children had expressed sentiments to various people that if the father would only die his wealth would be distributed among them, and these facts were conveyed to decedent, would you say that the decedent's belief in this regard was an insane delusion and the idea of an insane man?

A. If that fact were established I would say that it was not unreasonable.

Q. I am asking you to assume that fact, am I not?

A. Yes.

Q. All the other facts upon which you base your conclusion were assumed and not proved, is that not correct?

A. That is true.

Q. And it is correct, therefore, is it not, that if the decedent's belief concerning his children's wish that he die and that the decedent's refusal to see these four children had a basis in fact and reason, that you would come to a different conclusion with respect to the insanity of the decedent?

A. I would be compelled to do that.

Q. If any of the three factors which you concluded were an essential basis for a conclusion of insanity did not in fact exist, you would say that the decedent was sane, is that not true?

A. I would have to.

The expert should see the hypothetical question before he takes the stand. Especially is this true if it is lengthy, for counsel for the adverse

side may ask the physician to repeat it or to repeat the facts which the physician feels are essential for the opinion. The physician should discuss the hypothetical question with counsel before the trial. He should determine and advise counsel what are the essential and the non-essential facts.

4. A cross-examination as to physician's fees or compensation is quite a frequent occurrence. In connection with a case involving personal injuries such cross-examination follows:

Q. Did you come to court today pursuant to subpoena?

A. No, I did not.

Q. You came voluntarily, merely as a result of a telephone call or an oral request?

A. Yes.

Q. You expect a fee for testifying in court today?

A. Yes, I hope that I will receive one.

Q. Do you expect to be paid?

A. Yes, I do.

Q. Have you had any conferences with counsel or with the plaintiff with respect to fees for attending court?

A. No.

Q. No fee has been fixed yet?

A. No.

Q. Who asked you to come to court?

A. Mr. Blank (counsel for plaintiff).

Q. Did you see Mr. Blank before he called you?

A. He came up to see me at my office about three weeks ago.

Q. Was the subject of fees for your appearance today broached at all?

A. No, it was not.

Q. When did Mr. Blank call you on the 'phone about coming to court?

A. Yesterday.

Q. Was the subject of fees or money for your appearance in court discussed over the 'phone by Mr. Blank?

A. No, it was not.

Q. Did you ever have a talk concerning fees for appearing in court with the plaintiff?

A. No.

Q. When Mr. Blank called you to ask you to come to court, did you say anything about being paid for coming to court?

A. No.

Q. As a result of your appearance here in court you have been unable to visit a number of patients and thus you will suffer a financial loss by testifying?

A. That is true.

Q. When you stated that you would appear in court, you knew that you would suffer a financial loss unless you were paid for this court appearance?

A. Yes.

Q. But notwithstanding that, nothing whatsoever was mentioned about your fee by you or Mr. Blank, is that correct?

A. That is true.

A physician as an expert is privileged to charge a fee for expert testimony. An ordinary witness cannot demand compensation for testifying. Physicians sometimes fear that they cannot admit that they have been paid or promised a fee for a court appearance. Knowing that it is proper to receive compensation should make it possible for the physician, who is aware of this fact, to defend himself against this standard pattern of cross-examination. Where physician's records as to fees—the charges made and the payments received and the number of house and office visits—are not accurately kept, he can expect trouble from an inquiry along these lines. The remedy is quite simple—better records. Where the physician anticipates that the case will end in court, the records should be kept with an eye toward cross-examination. Nine times out of ten the history will reveal this.

The preceding examples were given to illustrate “standard patterns of cross-examination” affecting subject matter. A “standard pattern” can relate to the field of inquiry or the manner of questioning a witness.

A cross-examination as to details is a “standard pattern of cross-examination”—it is a way of questioning a witness. It may be pursued in any field of inquiry. A cross-examination as to details is probably the most frequent method utilized by cross-examiners. The phrase “standard pattern of cross-examination as to details” is intended to describe a cross-examination concerning all the details or particulars of any situation. The inquiry will search into every nook and corner and every
se of a subject. Usually, the cross-examiner hopes by pursuing this

method to test either the memory or the trustworthiness of the witness. The theory behind a cross-examination as to details is that if a witness did not actually live through the experiences claimed to have occurred, he will not be able to consistently or cohesively manufacture or create or imagine the details as fast as the questions are asked. A cross-examination of this character is designed to develop inconsistencies, contradictions and improbabilities in the witness under examination or between that witness and others who have testified. This is a "standard pattern" that may take place in practically any field of inquiry. An examination of this variety may necessitate a long and protracted questioning before any results are achieved. If a cross-examination as to details is had as to visits and treatments (where counsel suspects that the number of visits and the extent of the injuries are exaggerated), the cross-examiner may question the physician as to these matters: what complaints were made by the patient and what treatments were administered on each visit, the exact respects in which the plaintiff's complaint and condition differed on each visit, in what respect each treatment differed from each other, exactly what entries were made on each visit covering each complaint, finding and treatment, exactly when each medicine or treatment was discontinued, when each injury healed, duration of each visit. An inquiry into all these items would be made in the most minute detail. A case illustrating a cross-examination as to details follows. These physician's records contained full particulars of the patient's first visit and they set forth the date of each subsequent visit, but there was nothing in the records regarding the patient's complaint or the doctor's findings or treatment on any visit following the initial examination. Notwithstanding this, the doctor testified in quite minute detail as to the patient's complaints and the physician's own findings and treatment on numerous occasions that he saw the patient. The patient sustained what appeared to be a pretty usual garden variety of fractured arm. The doctor saw the patient twenty (20) times. He recalled special findings, complaints and treatments prescribed on eight of these, including the first visit. After thoroughly questioning the doctor as to everything that occurred on each visit, the cross-examination took this tack:

Q. The plaintiff suffered from a simple fracture of the left arm, is that correct?

A. Yes.

Q. Are the records that you produced and exhibited to me the only records that you have regarding this case?

A. Correct.

Q. Was there anything extraordinary or unusual about this fracture and if so will you describe it?

A. No, there was not.

Q. The last visit was made two years ago, is that correct?

A. Yes.

Q. Was there anything striking or outstanding about this case that makes it stand out in your mind above all others, and if so, describe what that is?

A. No, I wouldn't say that there is.

Q. I suppose that on the average you have treated at least ten patients per day during the last two years?

A. Probably more.

Q. Have you an equally good recollection as to the cases of all your patients?

A. Yes, I have a pretty good memory.

Q. That means that you have treated on the average about sixty patients per week?

A. Yes.

Q. Since the time that you treated the plaintiff you have had occasion to make at least 6,000 visits?

A. Yes, I suppose so.

Q. And can you recall the exact complaints made to you and the exact findings made by you, and the exact treatment administered by you on each of those 6,000 visits, with the same detail that you were able to recall these things with respect to the plaintiff?

A. No, I can't say that I could.

Q. Do you recall the names of any patients you saw on the same days that you saw the plaintiff?

A. No.

Q. Can you tell us what complaints were made to you or what findings were made by you, or what treatments were administered by you to any patients that you saw on the days that you saw this plaintiff?

A. No, I can't.

Q. Doctor, have you really and honestly an independent recollection as to what you were told by the plaintiff, and as to what you saw and did on each visit following the first examination, or did you tell us what is usual and customary in fractures of this kind?

A. Well, it may be that I am stating what the usual findings and treatment are for cases of this kind.

At this point more than any other, the advice concerning the statement "I don't know," and "I do not recall," bear repetition. If a witness blithely details what no human being can remember, the person will be branded as a liar.

Every subject upon which a doctor may be questioned can not be set forth in an article of this length. However, there are a few fields of inquiry and methods of examination which should be mentioned—even though they are not discussed fully—in an attempt to set forth the minimum that every physician should know about cross-examination:

1. *Medical Texts:* Prior to the trial, lawyers sometimes gather together medical texts concerning statements which support the propositions for which they are contending and which may differ from what the medical witness is likely to maintain. The physician will be confronted with these "medical authorities" on cross-examination. Before coming to the court the doctor should read up on the subject upon which the examination will be had and familiarize himself with names and authors of medical works in the field and know what books are considered authorities. This rehearsal will enable the physician to convincingly disagree with the medical texts where the statements made therein are unfounded and will enable the physician to support his contentions by books or printed authorities, which always influence court and jury.

2. *Extent of Court Work:* Lawyers will invariably ask a medical witness how much time he spends in court, how frequently he testified, whether or not he is customarily called for plaintiffs or defendants, the type of cases to which he is most often asked to appear and how often the physician has come to court for counsel in the case. The best defense to this line of inquiry is to know what is coming—and it generally does.

3. *Relationship between Physicians and Lawyer and Patient:* The

lawyer will explore into the length of time that the witness knows counsel and patient, whether the doctor forwarded the case to the lawyer, how friendly the parties are, and the like. The cross-examiner's design is to show that the doctor is not a disinterested witness and that the testimony is colored by friendship. This line of cross-examination is not as effective with the triers of the facts as counsel ordinarily believes. The advice given under the heading "*Extent of Court Work*" applies with equal force here. To be forewarned is forearmed.

4. *Subjective Symptoms*: Where the patient's injuries or principal injuries are largely subjective, the physician can expect from a competent cross-examiner a strenuous cross-examination about the matter. The cross-examination will first determine what are the subjective symptoms, what are partly subjective and what the doctor actually saw or found. The cross-examiner will endeavor to find out what exists solely in the patient's mind and what can be established by objective findings. Since cross-examination is designed to test the truth it cannot be expected that "tricks" can be taught to evade its effect. A remedy for this does exist and that is a more thorough examination of the patient by the physician and more complete and careful records. Whenever an appearance in court is a possibility, the physician should remember that he will be questioned as to what complaints and injuries are subjective symptoms.

5. "Have you talked with anybody about this case?" is a common question. Laymen "fall" for this quite frequently. Physicians only rarely. The usual pattern of this cross-examination is in this form:

Q. At any time before today did you discuss this matter, or the testimony that you have just given with any person?

A. No.

Q. Did you ever discuss this matter with the attorney who just questioned you?

A. No.

Q. You testified on direct examination that you personally witnessed the automobile accident?

A. Yes.

Q. At any time did you discuss with the attorney who questioned you the facts or details as to what you saw?

A. No.

Q. Will you please then explain to this court and jury how that

attorney knew what you were going to say, or was aware of the fact that you saw this accident?

A. No answer.

Naturally this witness will be discredited in the eyes of the tribunal. Each and every juror is fully aware of the fact that this witness did talk with the party who questioned him, or with his attorney, or with somebody. Unless he had given his name to some person and told what he knew, he would not have been called as a witness. The witness was undoubtedly of the opinion that it was wrong or improper for a witness to talk with anybody concerning the matter. It is perfectly proper for a witness to talk with any person in advance of the trial. As a matter of fact the witness should go over the matter with the attorney who calls him before he appears in court, and he should ask the attorney to cross-examine him in the same way that the witness will be cross-examined on the trial. Likewise the witness should thoroughly familiarize himself with each and every angle of the case about which the cross-examination can be anticipated, and especially regarding all the facts that may appear to be unfavorable to the side for which the witness is being called. It is not wrong to prepare oneself thoroughly for trial.

Preparation is the key to success for the medical witness. A lawyer prepares for cross-examination. Why should the physician do less in anticipation of this mental duel? The physician's preparation should commence with the examination of the patient and with the making of the medical records of the case. Both should be made with an eye toward the trial. Before the trial a study should be made of the subject matter of the pertinent texts and the authorities should be examined. Conferences with the patient and the lawyer before testifying are most desirable. If all these instructions are followed the doctor will step up to the witness stand ready to devour the blood of the cross-examiner.

SIR FREDERICK GRANT BANTING*

CHARLES H. BEST

*Director, Department of Physiology and Banting and Best Department of Medical Research
University of Toronto*

BANTING will always be remembered primarily for the preëminent part he played in the discovery of insulin and I feel that you will wish me to speak particularly of that phase of his brilliant career.

Banting's ancestors were of Irish and Scotch extraction. I remember a very pleasant week end spent with him and his parents at their farm house shortly after the first stage of the insulin work was completed. His mother, whose maiden name was Grant, died only a year before her son. Both she and his father were of sterling worth. I have a letter from Banting written in answer to a note of condolence at the time of his mother's death. He wrote "The death of our parents places us in the front line."

After qualifying at the High School in Alliston, where he was born, Banting entered the University of Toronto. He was the type of student whom his instructors remembered. He had an inquisitive mind. His medical course was interrupted by the Great War but after enlisting as a private, he was sent back to obtain his degree. He completed his course in 1917 and immediately entered the Army. He took a very great interest in his military patients and many of them kept in touch with him throughout his life time. The high point of his military career was his experience in France, where he won the Military Cross for bravery in action.

After the war he specialized in surgery at the Sick Children's Hospital in Toronto, where he gained the friendship of such men as the late Professor C. L. Starr, Professor W. E. Gallie and Dr. D. E. Roberston. When Banting left the Sick Children's Hospital he began the practice of medicine in London, Ontario. The growth of his practice was disappointingly slow and Banting spent some time demonstrating in the Department of Physiology of the University of Western Ontario. While preparing a lecture on diabetes, he read an article by Dr. Moses Barron.

*Read October 2, 1941 at the Stated Meeting of The New York Academy of Medicine.

Banting always felt that Dr. Barron, whom I think he subsequently met, had helped him to form an hypothesis which was in part responsible for the initiation of the work which led to the isolation of insulin.

Banting went to Toronto in the autumn of 1920 to consult Professor J. J. R. Macleod who was recognized as one of the world's greatest authorities on carbohydrate metabolism. I was spending part of my time that year in physiological research under Macleod's direction but I did not meet Banting until the next spring just after I had completed my course in Physiological and Biochemical Sciences. Macleod told me about Banting's desire to search for the internal secretion of the pancreas and he spoke admiringly of Banting's determination. This quality was the outstanding one in his character and was immediately apparent when I met him in May, 1921, a few days before the investigations which resulted in the isolation of insulin were begun. The initiation of the work was due entirely to him and he overcame all of the many obstacles in his path.

It will perhaps serve as a further appreciation of his character if I outline a few of the incidents which seemed to us important at the time. When the first five weeks of work revealed the fact that our technique for securing pancreatic degeneration was unsatisfactory, Banting did not hesitate to finance himself for a further period by selling his small car. He sometimes performed minor operations for some of his medical colleagues. He loaned me a small sum which was only repaid when Professor Macleod in the autumn made arrangements for us each to receive the sum of \$60 monthly. My payments and, I think, Banting's were dated back for several months.

Banting was a skilful and resourceful surgeon. For the first few months all of the chemical work fell to my lot but he gradually learned the techniques and he taught me the surgical procedures essential to our work. There were, of course, many problems but our association during those busy months gave me a tremendous respect for his perseverance and peculiar ability to plan attacks and to carry through the investigation. We became very firm friends. His letters to me and the charts and illustrations for our first articles which we worked on together, are among my most prized possessions. I will always be indebted to him for his generous references to my part in the insulin investigations, for sharing equally with me his half of the Nobel Prize award and for his numerous demonstrations of thoughtfulness and regard. At the last com-

mittee meeting which we attended together, a few weeks before his death, an extension of my department was under consideration by members of our Board of Governors. Banting's unselfish and most helpful interest in this matter is recorded in the minutes of that meeting.

Our very intimate association in research, which began on May 16, 1922, persisted until October 1923, when I decided to proceed with my medical course. Shortly after that the Banting and Best Department of Medical Research was created and Banting was installed as Director. He worked very hard at numerous problems over the period of sixteen years until the present war was upon us. He devoted himself mainly to cancer research but found time to stimulate many young associates who attacked a great variety of problems. The work on silicosis was perhaps the most successful.

I firmly believe that his second great contribution was made in the eighteen months of war when he sacrificed all his personal interests and gave himself unsparingly to organizing our country for research in the various aspects of war medicine. He devoted himself primarily to the medical aspects of aviation and eventually, as you all know, gave his life while attempting to carry new information on these problems to England.

Banting was a man of exceptional physical courage, intense determination, and warm friendships. He achieved the distinction of becoming our most illustrious Canadian citizen. He will be commemorated in many ways but he would have asked nothing more than that every attempt be made to extend and apply the results of the work which he began.

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London, Methuen, [1942], 338 p.
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PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETING

MAY 21—*The Harvey Society (in affiliation with The New York Academy of Medicine)*. The Eighth Harvey Lecture, "The Comparative Anatomy and Pharmacology of the Pituitary Body," Eugene M. K. Geiling, Professor of Pharmacology, University of Chicago Medical School. Report on election of Academy Fellows.

SECTION MEETINGS

MAY 1—*Surgery*. ¶ Executive session—a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee: for chairman—Frank J. McGowan, for secretary—John V. Bohrer, For member of Advisory Committee—Frank B. Berry. ¶ Presentation of cases—a] 1. Tuberculosis of the appendix, 2. Friedländer's bacillus pneumonia with secondary lung abscess. Operation—Recovery, D. Rees Jensen; b] Cases of diabetic gangrene. Healing under conservative therapy (lantern slides), Saul S. Samuels. ¶ Paper of the evening—The topical use of sulfanilamide and sulfadiazine in various media in the treatment of burns, Adrian V. S. Lambert. ¶ General discussion.

MAY 5—*Dermatology and Syphilology*. ¶ Presentation of cases—a] Beth Israel Hospital; b] Brooklyn Jewish Hospital; c] Cornell University Medical College. ¶ Discussion. ¶ Executive session—Election of Section Officers and member of Advisory Committee: for chairman—Frank C. Combes, for secretary—Samuel M. Peck, for member of Advisory Committee—Eugene F. Traub.

MAY 5—*Combined Meeting: Neurology and Psychiatry and the New York Neurological Society*. Reading of the minutes. ¶ Papers of the evening—a] The electroencephalogram in epilepsy, Francis

A. Echlin, discussion by Paul Hoefler, Margaret Rheinberger, Ph. D. (by invitation); b] A psychopathological review of senile and arteriosclerotic disorders, Oskar Diethelm (by invitation), discussion by John H. Travis; c] Mental cachexia: Nature and management, John L. Smalldon (by invitation), discussion by Leland E. Hinsie, Howard W. Potter. ¶ Executive session of the Section—Election of Section Officers and member of the Advisory Committee: for chairman—Charles Davison, for secretary—Gerald R. Jameison, for member of the Advisory Committee—George H. Hyslop.

MAY 13—*Historical and Cultural Medicine*. ¶ Executive session—a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee: for chairman—Herman Goodman, for secretary—Edward F. Hartung, for member of Advisory Committee—Claude E. Heaton. ¶ Paper of the evening—Hand and occupation: A study in the history of occupational medicine, George Rosen (by invitation), discussion by Leonard Greenburg, Louis Tulipan. ¶ General discussion.

MAY 14—*Pediatrics*. ¶ Executive session—a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee: for chairman—Charles Hendee Smith, for secretary—Edith M. Lincoln, for member of Advisory Committee—Alfred G. Langmann. ¶ Presentation of single case reports—a] Babies Hospital, refractory rickets, Donovan J. McCune (by invitation), Beridge Robertson (by invitation); b] Beth Israel Hospital, Edema with unexplained hypoproteinemia, lipemia and eosinophilia, Jean Wolfson (by invitation); c] Bronx Hospital, hepatic necrosis, Henry Weisman (by invitation); d] Lenox Hill Hospital, Subdural hematoma, Julian L. Rogatz; e] Mount Sinai Hospital, Trichobezoar of

the stomach, Philip J. Kresky (by invitation); f] New York Hospital, A rare congenital anomaly of the lung, Samuel W. Dooley (by invitation); g] New York Post-Graduate Hospital, Pseudohermaphroditism in a case of adrenal hyperplasia, Vincent de P. Parkin (by invitation); h] Roosevelt Hospital, Hypoglycemia convulsions with subtotal pancreatectomy, Agnes G. Wilson (by invitation), Howard A. Patterson; i] New York Infirmary for Women and Children, Primary tuberculosis of the conjunctiva, Margaret Sedam (by invitation), Olga Sitchevska (by invitation); j] Beth Moses Hospital, Glycogen storage disease with cardiomegaly, Harry Wexler, Abraham R. Kantrowitz; k] Bellevue Hospital, Multiple osteomyelitis of the new born, Samuel Stone (by invitation); l] Willard Parker Hospital, Asthma with pulmonary tuberculosis and compression of the vagus nerve, Nicholas F. Fiegoli (by invitation), Theodore Ehrenreich (by invitation).

MAY 15—*Orthopedic Surgery*. ¶ Executive session—a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee: for chairman—John C. McCauley, Jr., for secretary—Halford Hallock, for member of Advisory Committee—Joseph Buchman. ¶ Papers of the evening—a] Paget's disease—a new theory of etiology and its relationship to vitamin C, Frederick R. Thompson, discussion by Mather Cleveland, David M. Bosworth, and Samuel Kleinberg; b] A new approach to the diagnosis of herniation of intervertebral discs, William R. Duncan (by invitation), discussion by Lewis Clark Wagner and Kenneth M. Lewis; c] Tuberculosis of the greater trochanter and adjacent bursae, Joseph B. L'Episcopo, Edward Haggerty (by invitation) and David M. Bosworth; d] Osteitis pubis—report of a case in a woman, Samuel Kleinberg.

MAY 18—*Ophthalmology*. ¶ Instruction hour: 7:00 to 8:00 o'clock—a] Binocular oph-

thalmoscopy and red-free light in fundus diagnosis—Ralph I. Lloyd; b] Clinical meeting; ¶ Executive session: 8:30 o'clock—a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee: for chairman—Daniel B. Kirby, for secretary—Richard T. Paton, for member of Advisory Committee—Kaufman Schlivek. In memorandum—Henry Robertson Skeel, W. Guernsey Frey. ¶ Presentation of cases—a] A case of congenital anterior synechiae, corneal opacities and microphthalmos, Frederick H. Theodore; b] A case of tumor of the optic nerve, William B. Agan (by invitation); c] Cases of congenital absence of lacrimal puncti. Three cases in the same family, Arno E. Town (by invitation); d] A case of reconstruction of the lower eyelid—Bernard Fread; e] A case of thrombosis of the central vein treated with heparin, Charles M. Rosenthal (by invitation); f] A case of modification of Wheeler's tarsorrhaphy—Daniel B. Kirby; g] A case of congenital prepapillary cyst, Jesse M. Levitt (by invitation); h] A case of bilateral pigmentation of the retina with macular changes, Gerald T. Schwarz (by invitation); i] A case of epithelioma of the cornea, George N. Wise (by invitation).

MAY 19—*Medicine*.—¶ Executive session—a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee: for chairman—Irving S. Wright, for secretary—Martin Henry Dawson, for member of Advisory Committee—Asa L. Lincoln. ¶ Papers of the evening—a] The metabolism of the human sperm in relation to survival and fertility (with moving picture demonstration), John McLeod (by invitation); c] Discussion by Ephraim Shorr (by invitation).

Genito-Urinary Surgery. The following were elected at the April meeting of the Section: chairman—Frank P. Twinem, secretary—John H. Rathbone, member of Advisory Committee—John H. Morrissey. No meeting of the Section was

held due to the meeting of the American Urological Association in New York, June 1-4.

Neustaedter, discussion by George Panicolaou (by invitation). ¶ General discussion.

MAY 20—*Otolaryngology*. ¶ Executive session—a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee: for chairman—John Winston Fowlkes, for secretary—Victor Carl McCuaig, for member of Advisory Committee—Page Northington. ¶ Papers of the evening—a] Technique of planigraphy of the larynx, Murray M. Friedman (by invitation); b] The mechanism of phonation from the viewpoint of planigraphy of the larynx, Bruno L. Griesman (by invitation); c] Discussion, John D. Kernan. ¶ Case reports—a] Petrositis; paralysis of the 6th and 7th nerves; meningitis, pneumococcus Type III, Thomas G. Tickle; b] Horner's syndrome with chronic purulent otitis media: demonstration of diagnostic test, Louis Hubert; c] Laryngectomy for extrinsic cancer, Mervin C. Myerson.

MAY 26—*Obstetrics and Gynecology*. ¶ Executive session—a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee: for chairman—William T. Kennedy, for secretary—Locke L. Mackenzie, for member of Advisory Committee—Harry Aranow. ¶ Papers of the evening—a] A simple safe maneuver for the delivery of shoulders, Charles Edwin Woods (by invitation); b] The termination of pregnancy in patients with toxemia, Irving A. Bunkin (by invitation), Jefferson J. Vorzimer (by invitation), Edwin G. Langrock; c] Value of the endometrial biopsy as compared with the vaginal smear, Locke L. Mackenzie, Theodore

AFFILIATED SOCIETIES

MAY 18—*New York Roentgen Society (in affiliation with The New York Academy of Medicine)*. ¶ Symposium of cancer of the breast—a] Autopsy findings, Angelo M. Sala (by invitation), Elma Barany (by invitation); b] Indications for radical mastectomy, Cushman D. Haagensen (by invitation), Arthur Purdy Stout (by invitation); c] Roentgen therapy of the primary tumor and axillary metastases—inoperable and pre-operative cases, Maurice Lenz; d] Roentgen therapy of distant metastases, Jacob R. Freid and Henry Goldberg (by invitation). ¶ Discussion by Hugh Auchincloss (by invitation), William C. White (by invitation), William Harris and Haig Kossabach. ¶ Executive session.

MAY 28—*New York Pathological Society (in affiliation with The New York Academy of Medicine)*. ¶ Presentation of cases—a] Periarteritis nodosa in scarlet fever, Vera B. Dolgopol, S. Spector (by invitation); b] Myocardial lesions in myasthenia gravis, Antonio Rottino, Robert Poppiti (by invitation). ¶ Papers of the evening—a] The origin of colloid in lipoid droplets in the epithelial cells of the renal tubules, Hans Smetana; b] Morphogenesis and significance of verrucal endocarditis (so-called terminal endocarditis or non-bacterial thrombotic endocarditis), Arthur C. Allen, Jonas M. Sirota (by invitation) ¶ Executive session.

DEATHS OF FELLOWS

BUCKLEY, ROBERT EMMETT: 50 East 63 Street, New York City; born in Connecticut in 1888; died in New York City, July 25, 1942; graduated in medicine from Yale University School of Medicine in 1911; elected a Fellow of the Academy January 3, 1929.

Dr. Buckley was director of surgery in otolaryngology to the Manhattan Eye, Ear and Throat Hospital and consulting otolaryngologist to the Misericordia and Roosevelt Hospitals. He was a Fellow of the American Medical Association, a diplomate of the American Board of Otolaryngology, a member of the American Academy of Ophthalmology and Otolaryngology, the American Laryngological Association, the American Laryngological, Rhinological and Otolological Society, and the State and County Medical Societies.

CHAPIN, HENRY DWIGHT: Bronxville, New York; born in Steubenville, Ohio, February 4, 1857; died in Bronxville, June 27, 1942; received from Princeton University the de-

gree of B.Sc. in 1877 and M.A. in 1886; graduated in medicine from the College of Physicians and Surgeons in 1881; elected a Fellow of the Academy February 4, 1886.

Dr. Chapin was emeritus professor of pediatrics at the New York Post-Graduate Medical School, Columbia University; one of the founders and on the staff of the Children's Welfare Federation; a member of the American Pediatric Society, a Fellow of the American Medical Association, and a member of the State and County Medical Societies.

HELLER, ISAAC MORRIS: 115 East 61 Street, New York City; born in New Haven, Connecticut, May 20, 1872; died in New York City, June 7, 1942; graduated in medicine from Yale University School of Medicine in 1896; elected a Fellow of the Academy January 6, 1910.

Dr. Heller was a member of the medical board and attending otolaryngologist to the Lebanon Hospital, a major in the medical branch of the Officers Reserve Corps, a Fellow of the American College of Surgeons, a Fellow of the American Medical Association, a diplomate of the American Board of Otolaryngology, a member of the American Laryngological, Rhinological and Otolological Society and a member of the State and County Medical Societies.

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| | |
|--|----------------------|
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| <i>Tidal drainage and cystometry in the treatment of the bladder in the presence of spinal cord injuries</i> | Donald Munro |
| <i>Diagnosis and treatment of brain abscess</i> | Joseph E. J. King |
| <i>Differential diagnosis and prognosis of brain tumors</i> .. | Gilbert Horrax |
| <i>Certain abnormalities of ocular movements: their importance in general and neurologic diagnosis</i> | Frank B. Walsh |
| <i>Wounds and injuries of the spinal cord</i> | Byron P. Stookey |
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| <i>Multiple sclerosis and "encephalomyelitis"</i> | Tracy J. Putnam |
| <i>Limitations of vitamins in neurology</i> | Charles D. Aring |
| <i>Present status of shock therapy</i> | Nolan D. C. Lewis |
| <i>Prefrontal lobotomy</i> | Walter Freeman |
| <i>Types of psychotherapy and indications for them</i> | Lawrence S. Kubie |
| <i>Migraine and other forms of headache</i> | Henry A. Riley |
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IN THEIR CONTRIBUTIONS

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE



NOVEMBER, 1942

MARIHUANA *

ROGER ADAMS

Professor of Chemistry, University of Illinois

Harvey Lecture, February 19, 1942

THE facts on marihuana which I shall present to you this evening comprise the results of the coöperative efforts of three laboratories—the chemical investigations at the University of Illinois, the pharmacology at Cornell Medical College under the direction of Dr. S. Loewe, and the clinical experiments at Welfare Island Hospital under the auspices of the Mayor's Committee on Marihuana and under the immediate direction of Dr. Samuel Allentuck. All three laboratories acquired their supplies of raw materials from Dr. H. J. Wollner of the Narcotics Laboratory of the Treasury Department, and received much encouragement and stimulation from him. Dr. J. R. Matchett of the same laboratory contributed significantly to the general problem by devising a method whereby a fraction of the red oil of hemp, containing a very high concentration of the active principle, could be obtained.

Cannabis sativa, more commonly called hemp, is of peculiar interest. It has been known for thousands of years as a product of commerce; the fiber of the plant for clothing and rope, the seeds for the oil they

* From the Noyes Chemical Laboratory, University of Illinois,* the Department of Pharmacology of Cornell University Medical College and the Welfare Island Hospital.

contain. The presence of an intoxicating principle in the resin of the plant has also long been recognized, since the physiological action of hemp preparations is mentioned in some of the earliest records available and is described in the first medical treatises. In the last two thousand years over four hundred articles have been published describing its intoxicating characteristics and the effects on humans.¹

The preparation of the hemp for consumption as an intoxicant varies in different countries and consequently several names, such as marihuana, charas, ganja, hashish, and others, have been adopted, each in a definite locality. It is significant that the same characteristic phenomenon from any of these products is observed in man when the doses are equated.

The clarification of the chemical and medical aspects of hemp extracts has been extraordinarily slow for a material known as long and used as frequently as marihuana. The reasons have been several—the failure of chemists to isolate a pure active principle, the unsuccessful attempts of the pharmacologist to find an animal test which paralleled the activity in humans, and finally the lack of controlled clinical experiments.

The recorded medical literature is most confusing. The reports are contradictory, and the description of the drug varies from one which is habit-forming and which with constant use is as harmful to the system as morphine, to one which is almost completely innocuous with a stimulation not far remote from that of alcohol. Spread of the use of marihuana in the United States has been due in part to its ready availability, since hemp grows wild in countless places all over the country. Newspaper articles have described marihuana smoking among school children, and magazine articles have carried vivid accounts of activities encountered in tea-pads—dens where marihuana is enjoyed by devotees. Marihuana has been accredited with precipitating premeditated criminal acts, of lowering morals and releasing inhibitions, and of serving as a stepping-stone to other drug addictions such as the use of heroin. Furthermore, the claim has been made that continued use of marihuana produces mental deterioration. A "Marihuana Bill" was passed by the United States Congress in 1934. For purposes of administration marihuana is defined essentially as any part of the hemp plant or extract therefrom which induces somatic and psychic changes in man. The regulations and penalties in the bill for use and distribution

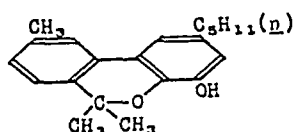
of marihuana are as rigid as those imposed for the use and sale of morphine.

In the investigations which are to be described this evening, more quantitative data on the chemistry, pharmacology, and clinical aspects of marihuana have been gathered than hitherto have been available and present a foundation for the eventual complete understanding of this interesting natural product. The chemical investigations, an excellent résumé of which up to 1938 has been published by Blatt,² will be discussed first. Practically all of the chemical experiments which have been reported were performed on the resin present in hemp from various sources and the same general procedure for isolating the resin has been used by all investigators in this field. After extraction with an organic solvent, filtration of the solution thus obtained, removal of the solvent and vacuum distillation of the residue, a highly viscous, physiologically active oil results, red in color and boiling over a wide range. Fractionation of the oil leads to the concentration of the active components in the portion boiling from 180-190° (1 mm.) which is commonly known as "purified red oil." This purified red oil usually used in the chemical studies has been shown definitely to be a welter of closely related substances which are very difficult to separate from each other and which occur in varying proportions dependent on the source of the hemp.

Between 1840 and 1895, most of the chemical investigations consisted in attempts to discover tests which would provide means of identifying a hemp extract. Numerous color reactions were reported, only one of which has received frequent application and until recently general acceptance. This is the so-called alkaline Beam test which is the purple color produced by treatment of a hemp extract with 5 per cent methanolic potassium hydroxide.³ From our chemical results and from an extensive investigation of agronomic varieties of hemp by Dr. Matchett⁴ it can be concluded that this test is not indicative of a substance with marihuana activity.

In 1895 Wood, Spivey, and Easterfield⁵ were able to isolate from "purified red oil" by means of a treatment with acetic anhydride, a crystalline acetate, which was removed from the residual oil and which could be purified in the normal way. Hydrolysis of this pure acetate resulted in a homogeneous viscous oil which these investigators called cannabinol. Until about a decade ago, when the fact was shown to be erroneous, cannabinol was accepted as the active principle of hemp.

CHART I



(Cannabinol, Cahn)

| Cannabinol | M.P. °C. | Cannabidiol | M.P. °C. |
|---------------------------------------|----------|--|----------|
| $C_{21}H_{30}O_2$ | 75-76 | $C_{21}H_{30}O_2$ | 66-67 |
| <i>p</i> -Nitrobenzoate | 165-166 | <i>bis</i> -3,5-Dinitrobenzoate | 106-107 |
| <i>m</i> -Nitrobenzenesulfonate | 127-129 | <i>bis</i> - <i>m</i> -Nitrobenzenesulfonate | 119-120 |
| Acetate | 76-77 | Oil | |
| 3,5-Dinitrophenylurethan | 220-222 | Oil | |
| Optically inactive | | $[\alpha]_D^{25} -125^\circ$ (ethanol) | |
| No alkaline Beam test | | Superb alkaline Beam test | |
| No marihuana activity | | No marihuana activity | |

These same investigators performed preliminary experiments on the structure of the cannabinol molecule. Further work on its chemistry was impeded by the fact that in spite of many attempts in different laboratories the isolation of cannabinol was not repeated until 1932. At that time Cahn⁶, an English chemist, again obtained this compound and completed a series of brilliant researches from the results of which he was able to establish the skeleton and the substituents in the molecule but was unsuccessful in determining the orientation of all the groups.

It was with this background that the chemical experiments were begun at the University of Illinois.* Attempts to isolate cannabinol from the purified red oil of Minnesota wild hemp by the procedure described by Cahn failed. Consequently, attention was turned to attempts to isolate a phenolic product, the presence of which was established by qualitative tests. Of the numerous reagents employed, 3,5-dinitrobenzoyl chloride reacted to give a crystalline compound which was readily removed from the residual oil and purified. It proved to be a *bis*-ester, the hydrolysis of which by an appropriate method gave a new substance which was termed "cannabidiol" because of the presence of two phenolic groups.⁷ It was isolated first as an oil but eventually was obtained as a crystalline solid. By developing a new procedure as a substitute for Cahn's method the isolation of cannabinol from this same oil was also accomplished, and for the first time cannabinol was induced to crystal-

* The experimental work of the series of researches at the University of Illinois was performed by the following students: B. R. Baker, C. K. Cain, J. H. Clark, Madison Hunt, Charles F. Jelinek, W. D. McPhee, D. C. Pease, C. M. Smith, R. B. Wearn and Hans Wolff.

lize.^{8*} The properties of cannabinol and cannabidiol are compared in Chart I. Cahn's proposed formula for cannabinol is shown; his evidence for this structure was conclusive except for the positions of the hydroxyl and *n*-amyl groups.

The similarity in the empirical formulas of these two compounds is striking and led to the belief that these two sister substances must have structural formulas not too unrelated. The optical activity of cannabidiol suggested immediately the probability of partial hydrogenation of one aromatic nucleus in cannabinol and indeed the left one, since cannabidiol contains phenolic groups.

Although cannabidiol, like cannabinol, is physiologically inactive, the study of its structure and its reactions was most revealing. The results served to determine completely the structure of cannabinol and led to the formation of tetrahydrocannabinols, products of high marihuana potency which are probably active principles in the red oil of hemp.

The complicated and extensive chemical investigations on the structure of cannabidiol, on the synthesis of cannabinol, and on the preparation of tetrahydrocannabinol and synthetic analogs, will be presented in very brief form and only the more significant facts will be mentioned. The structure of cannabidiol¹⁰ will be considered first with the pertinent reactions given in logical rather than chronological order.

Typical color tests indicated a phenol group, and formation of *bis*-esters and ethers the probable presence of two such groups. Catalytic reduction resulted in the absorption of two moles of hydrogen with formation of a molecule which still retained the two phenolic groups, thus leading to the deduction that two aliphatic double bonds were present. Pyrolysis of cannabidiol with pyridine hydrochloride caused cleavage into *p*-cymene and olivetol (1,3-dihydroxy-5-*n*-amylbenzene) both of which were identified by comparison with authentic samples. This is convincing evidence that cannabidiol is composed of dihydrocymyl and olivetol residues. The positions of the linkage between these residues were determined next. Cannabidiol was first reduced to tetrahydrocannabidiol and then oxidized; menthane carboxylic acid was isolated, identical with a specimen obtained by synthesis from l-menthol,

* Cannabidiol and cannabinol are the only pure compounds related by structure to the active constituents which have been isolated from hemp extracts. Claims have been made for the isolation of other compounds or their derivatives, but no detailed information is available and the results require confirmation.⁹

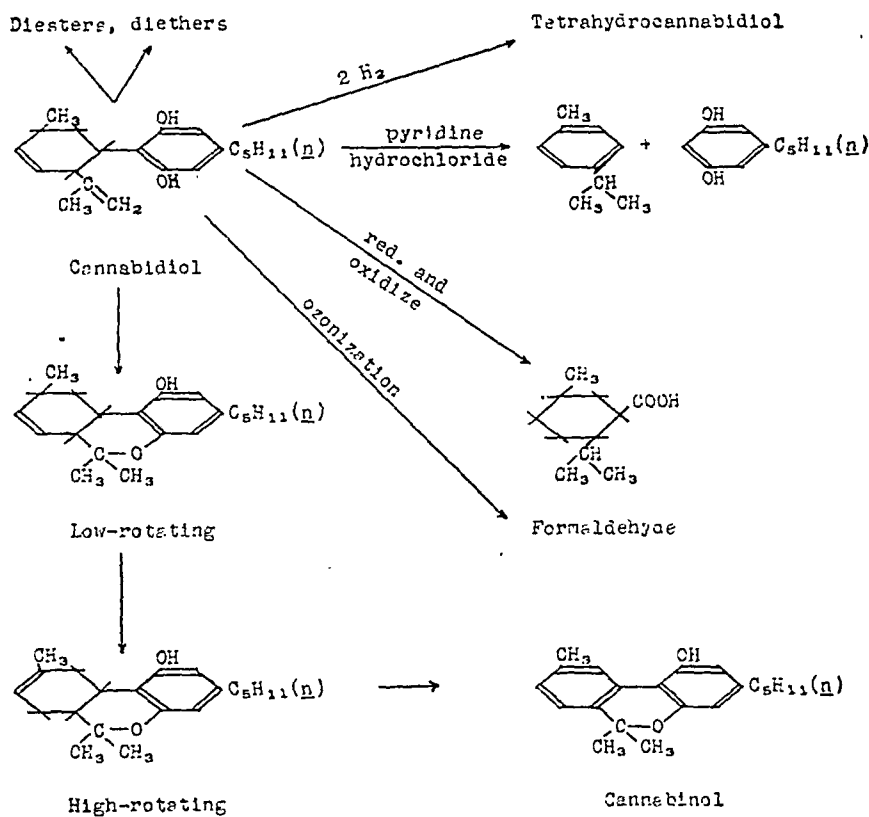


CHART II

thus demonstrating that the attachment of the dihydrocymyl residue was adjacent to the isopropyl grouping. From a comparison of the absorption spectra of various amyl resorcinols and of cannabidiol and its reduction product, the dihydrocymyl was postulated as being attached to the olivetol between the hydroxyl groups. Direct chemical proof of this was accomplished by conversion of cannabidiol with acidic reagents to tetrahydrocannabinol which, upon dehydrogenation, gave cannabinol. Cannabinol was shown to contain the linkage between the hydroxyls by synthesis of this molecule by an unequivocal method.

The structure of the cannabidiol molecule was thus established except for the orientation of the two aliphatic double bonds in the dihydrocymyl residue. One of these proved to be terminal, since ozonization of cannabidiol gave formaldehyde. This information, along with the fact that tetrahydrocannabinol was produced from cannabidiol through closure of a pyran ring, left no doubt that this terminal double

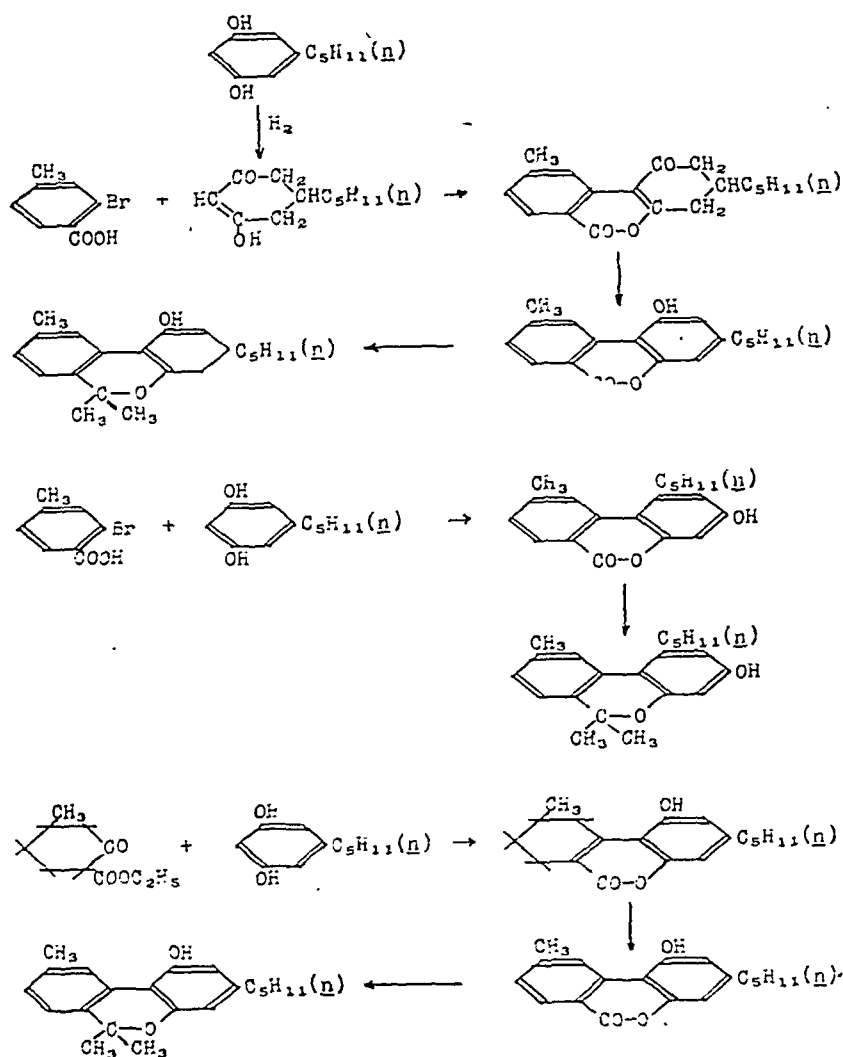


CHART III

bond must be present as an isopropenyl group. The location of the second double bond was determined only by indirect means. Since the arguments are rather involved, they will be omitted here and merely the positions assigned for the double bonds will be given. The tetrahydrocannabinol obtained in the isomerization of cannabidiol, varied in rotation dependent on the reagent used. Apparently two forms exist which were isolated as low-rotating and high-rotating isomers. In the low-rotating tetrahydrocannabinol, which presumably has the double bond in the same position as in cannabidiol, the double bond was deduced

to be in the γ,δ -position between the unsubstituted carbons; in the high-rotating isomer, the double bond is probably substituted in the γ,δ -position which includes the ring carbon holding the methyl group.

The establishment of olivetol as a cleavage product of cannabidiol revealed the probable orientation of the hydroxyl and *n*-amyl groups in cannabinol. This supposition was proven correct by the synthesis of cannabinol by two different methods¹¹ as shown in Chart III. The syntheses served also to prove that the position of the linkage of the two benzene rings is between the hydroxyl groups and thus confirmed a similar attachment of the rings in cannabidiol.

2-Bromo-4-methylbenzoic acid and dihydroolivetol condensed in the presence of alkali and a copper salt to 1-keto-3-*n*-amyl-9-methyl-1,2,3,4-tetrahydro-6-dibenzopyrone; dehydrogenation gave 1-hydroxy-3-*n*-amyl-9-methyl-6-dibenzopyrone which, with excess of methylmagnesium iodide, gave cannabinol, (1-hydroxy-3-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran). An analogous condensation of 2-bromo-4-methylbenzoic acid with olivetol, followed by treatment with methylmagnesium iodide, gave the isomeric cannabinol with the linkage between an hydroxyl and the *n*-amyl group. The second method consisted in condensation of ethyl 5-methylcyclohexanone-2-carboxylate with olivetol in the presence of phosphorous oxychloride to give 1-hydroxy-3-*n*-amyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone. Dehydrogenation to the corresponding 1-hydroxy-3-*n*-amyl-9-methyl-6-dibenzopyrone followed by treatment with methylmagnesium iodide gave cannabinol.

The disappointment accompanying the discovery that cannabidiol had no marihuana activity was more than compensated by the observation that both the low-rotating and high-rotating tetrahydrocannabinols possess very marked marihuana potency.¹² These two substances, which were high-boiling oils, have not yet been induced to crystallize. All attempts to isolate solid crystalline derivatives have failed. The isomerization of cannabidiol required intensive study before procedures were found which resulted in products of constant rotation. Apparently, without very specific conditions, mixtures of low- and high-rotating forms are obtained which cannot be converted readily to a product of maximum rotation. Tetrahydrocannabinol of constant rotation $[\alpha]^{27}_D -265^\circ$ can be produced conveniently from cannabidiol merely by heating the latter in benzene solution with a little toluene sulfonic acid until the reaction mixture exhibits no alkaline Beam test. This product was the

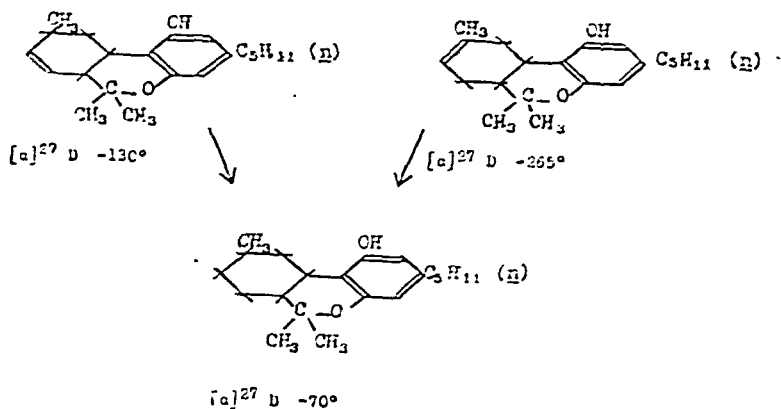


CHART IV

principal one selected for pharmacological and clinical investigation.

The acetates of these tetrahydrocannabinols also had marihuana potency though less than that of the unacetylated compounds. By catalytic reduction all of the tetrahydrocannabinols of varying optical activity gave a hexahydrocannabinol of essentially the same optical activity. This product was physiologically active though less so than any of the tetrahydrocannabinols from which it was derived.

The typical marihuana activity manifested by the isomeric tetrahydrocannabinols constitutes ponderable evidence that the activity of the plant itself, and of extracts prepared therefrom, is due in large part to one or the other of these compounds, or both, and possibly also to their stereoisomers, of which a number are possible. Confirmation of this supposition is available from an investigation by Wollner, Matchett, Levine and Loewe,¹³ the results of which were published just recently. These authors have described the isolation from acetylated red oil of a tetrahydrocannabinol acetate of potency greater than that of either of the tetrahydrocannabinols prepared by isomerization of cannabidiol. Partition of the acetylated red oil was accomplished by selective adsorption. Silica gel removed cannabidiol diacetate and unknown material from a benzene solution of the mixture; alumina adsorbed substances of lower rotation by two passages, first in carbon tetrachloride, then in pentane solution. The product was judged to be stereochemically homogeneous by failure to effect further separation through selective adsorption or by careful fractional distillation in a specially designed high-vacuum fractionating column. Hydrolysis of the acetate yielded a tetrahydro-

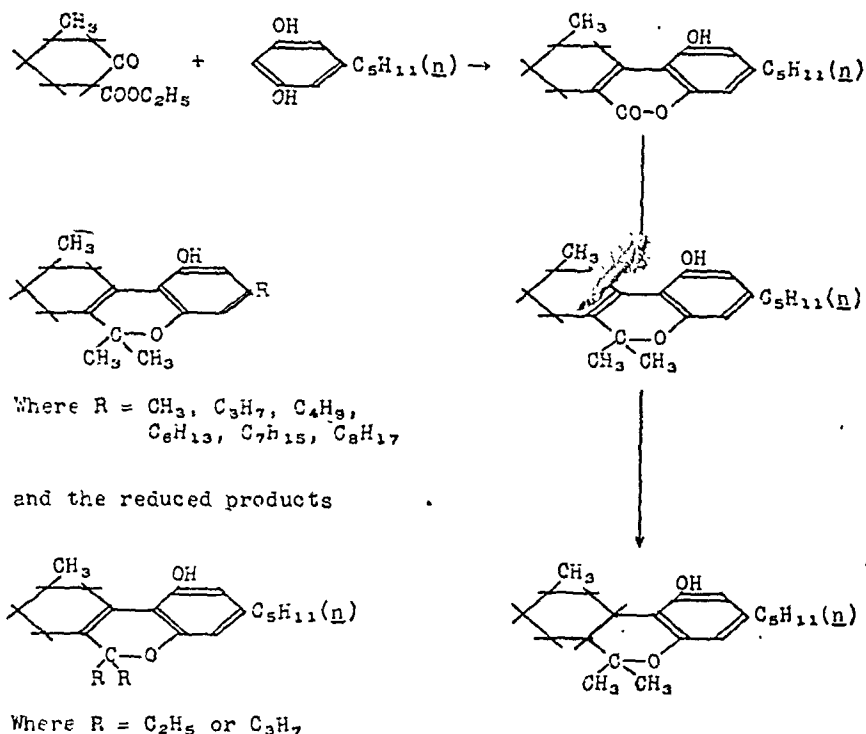


CHART V

cannabinol whose structure was identified through analysis and dehydrogenation to cannabinol. Its potency was similar to the products prepared by isomerization of cannabidiol. It would appear that rearrangement occurred during hydrolysis, since reacetylation failed to restore either the optical rotation or physiological potency to the original value.

With the discovery of the character of substances which possess marihuana activity, attention was directed next to attempts to synthesize compounds of similar activity. A very satisfactory procedure was devised for obtaining an isomer of the natural tetrahydrocannabinol with the double bond conjugated to the benzene ring. It consisted in the condensation of ethyl 5-methylcyclohexanone-2-carboxylate with olive-tol to give 1-hydroxy-3-*n*-amyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone which, with excess methylmagnesium iodide, yielded 1-hydroxy-3-*n*-amyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran.¹⁴ The product proved to have marihuana activity though only about one-tenth that of its isomer, natural tetrahydrocannabinol. A series of several closely related synthetic compounds was then prepared by the same

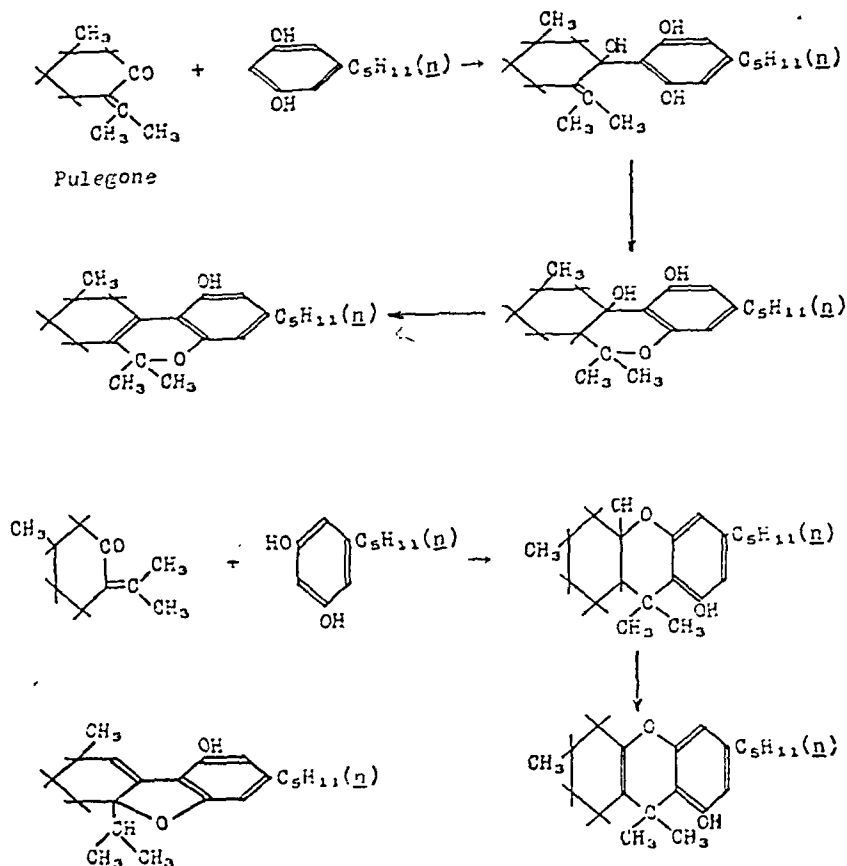


CHART VI

Homologs were prepared in which the *n*-amyl group was substituted by C₂H₅, C₄H₉, C₆H₁₃, C₇H₁₅, C₈H₁₇, C₉H₁₉; the reduction product of each was also synthesized.

procedure using the same keto ester but homologs of olivetol.¹⁵ All of these products were reduced to the corresponding hexahydro compounds.¹⁶ The synthetic tetrahydrocannabinol was also modified by replacing the 6-methyl groups by ethyl and propyl groups.¹⁷ (Chart V.)

A provisional synthesis designed to obtain an optically active tetrahydrocannabinol was sought in the condensation of pulegone and olivetol.^{17,18} In the presence of phosphorous oxychloride, a product which analyzes for, and has the properties of tetrahydrocannabinol is formed. A possible mechanism by which such a reaction might take place is shown in Chart VI. The purity of the final product is by no means established. There is a possibility of contaminants formed by condensation of the two reactants to give a partially hydrogenated xanthane

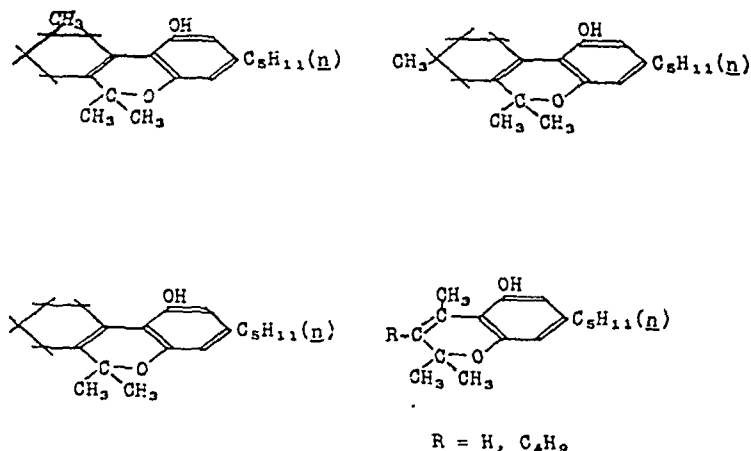


CHART VII

or a tetrahydrodibenzofuran, isomeric with tetrahydrocannabinol. Homologs in which the olivetol portion was substituted by other 1,3-dihydroxy-5-alkylbenzenes were synthesized.¹⁶ The reduction product of each was prepared.

Finally in Chart VII are shown molecules in which the left-hand ring has been modified by removal or by change in the position of the methyl group.¹⁷

The pharmacological studies on hemp extracts have been equally as meager as the chemical investigations and in the long history of *Cannabis* preparations only three tests have been reported. Liataud¹⁹ in 1844 observed that motor incoördination in the dog was a characteristic effect induced by marihuana preparations; Fraenkel²⁰ in 1903 interpreted this incoördination as a cataleptic condition. This was followed in 1928 by the observations of Gayer²¹ that in various animals such as cats, rabbits, or dogs, intravenous injection of marihuana preparations in acetone solution induced corneal anesthesia which was characteristic of active fractions of the resin. In 1937, Munch and Mantz²² reported no unequivocal effects when *Cannabis* preparations were administered to albino mice. On the other hand, Loewe²³ noted a definite increased depressant action when treated mice were given a hypnotic of the barbiturate series. Pernocton, butyl-bromoallyl barbituric acid, gave the greatest enhancement of any of the drugs tested.

The Gayer corneal anesthesia test was developed further by Marx and Eckhardt²⁴ but neither these investigators nor Gayer himself went further than to designate that the corneal reflex was normal or abnor-

mal. The corneal response was ascertained by tapping with von Frey hairs. Walton²⁵ took steps in a quantitative direction by counting the number of responses occasioned by tapping the cornea a given number of times and by plotting the results over the whole duration of the effect. By thus locating a definite maximum in the areflexia-versus-time curve of each experiment, quantitative comparisons were made possible by determining the ratios of doses producing equal maxima in different animals. Loewe²⁶ developed this procedure further by application of his method of "Bioassay by Approximation" to overcome as far as possible the large intra-individual and the large group variabilities which seem to be inherent in the reaction of all types of animals to marihuana preparations. His study of the Gayer test applied to the behavior of rabbits as test animals showed not only great inter-individual variations in sensitivity but also enormous intra-individual variations in the same animal. Using the same animal repeatedly, this investigator found a consistent decrease in sensitivity to one and the same dose. Therefore, even though the method of approximation was applied, the values of potency obtained by this method are not suitable for anything but qualitative purposes. Moreover, they do not parallel the dog-ataxia potencies of the same preparations, the divergence sometimes being tenfold. This indicates either that the Gayer test is not conclusive for quantitative measurements or else that an active principle other than that disclosed by the dog-ataxia test is present in red oil.

The "mouse sleep prolongation test" may be dismissed with merely a brief discussion. The *Cannabis* preparations, usually red oil, were administered by stomach tube. After a definite time, pernocton was injected intravenously at a level just above the threshold of hypnotic action. The synergistic effect of the *Cannabis* was measured by the period of suppression of the righting reflex averaged over all the animals of a single-dose group. This effect, though typical of red oil, could not be duplicated with the natural or synthetic tetrahydrocannabinols which had been shown definitely to have physiological activity in man. Pure cannabidiol, which is devoid of the marihuana effect upon man, showed the highest potency in this test and consequently the action from the red oil probably is due to its cannabidiol content.

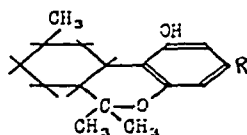
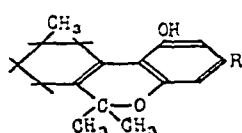
The determination of the cataleptic condition in dogs reported by Fraenkel, as accepted in former editions of the United States Pharmacopoeia for bioassay of *Cannabis* extracts, was developed further by

Walton²⁵ to attempt to make the effect the basis of a quantitative test. Six arbitrary stages of intensity of effects were recognized; first a slight depression; second, a barely detectable ataxia; third, an obvious ataxia; fourth, a marked ataxia in which the animal frequently pitches forward and barely catches itself; fifth, inability to stand alone; sixth, inability to rise and plunge about. The ataxia is chiefly a static one and is manifested particularly by swaying movements. Intravenous doses of red oil dissolved in acetone always acted within half an hour. A similar intensity of effect by oral administration required five to seven times the dose. Walton employed for evaluating potency the procedure used in most bioassay methods, the comparison of test and standard doses of equal intensity of effect. By comparing the results at various levels of dosage and by repeating the procedure a considerable number of times, he obtained more accurate results than had hitherto been reported. About eight trials with the unknown on the same dog, calibrated in about six trials with the standard, were used. A single assay required about three weeks or more for completion.

Loewe applied his principle of "Bioassay by Approximation" to the ataxia test and has thus been able to obtain a more decisive method for comparison of active products. The procedure aims at obtaining from each one of an adequate number of calibrated dogs, several figures of comparison of a test dose with the calibration doses. These figures represent ratios of doses, the response to which is not quantitatively the same. They are used to approximate the true potency value from both sides. At the same time the degree of overlapping marks the range of variation and gives an idea of the inherent inaccuracy. An entire assay may in this way be performed in a single day and highly consistent results may be obtained. The maximum order of accuracy is 10 per cent since this is the minimum of variation in the response of the same animal at different times. Since parallelism between the results of the dog-ataxia tests and the effects of the different preparations on humans has been established, it may be concluded that the ataxia method as developed by Loewe represents a reliable index of potency.

Using this procedure as just outlined, the comparison of results on the various natural and synthetic products will be presented in charts. Each value given represents the result obtained by the use of several dogs; three or four in the case of low potency materials, ten to twenty or more for substances of higher potency.

CHART VIII



R=*n*-alkyl

CH₃
C₂H₅
C₄H₉
C₆H₁₃
C₈H₁₇
C₁₀H₂₁
C₁₂H₂₅
C₁₄H₂₉
C₁₆H₃₃
C₁₈H₃₇

Potency

| Tetrahydro | Hexahydro |
|---------------|------------|
| 0.16 ± 0.03 | below 0.04 |
| .40 ± .08 | 0.26 ± .04 |
| .37 ± .12 | .37 ± .06 |
| standard 1.00 | .51 ± .08 |
| 1.82 ± 0.40 | 1.86 ± .37 |
| 1.05 ± .15 | 0.83 ± .13 |
| 0.66 ± .13 | .24 ± .06 |

Tetrahydrocannabinol [α]_D²⁵

-265° 7.3 ± 0.89
-260° 7.8 ± .78
-240° 7.6 ± 1.1
-165° 9.3 ± 2.9
-160° 8.23 ± 2.17
-126° 6.5 ± 0.65

Hexahydrocannabinol

-70° 3.0 ± 0.43

Parke, Davis and Company

Fluid Extract 0.060

American Fluid Extracts

thirty to forty different

samples varied in

potency .003-0.130

majority varied .019-.052

Purified red oil 1.24

Highly purified red oil
(Matchett) 4.33

In Chart VIII is shown a comparison of the potencies of the series of products analogous to synthetic tetrahydrocannabinol. The latter was adopted as a standard. The corresponding hexahydro derivatives were also tested. It is observed that the modification of the alkyl group results in a gradual increase in activity with increase in size until a maximum is reached at the *n*-hexyl derivative. The point of maximum potency is the same in the hexahydro compounds, though all, with the exception of the *n*-hexyl, exhibit a decreased effect. There is also presented the potencies of tetrahydrocannabinols of different optical rotations all derived from cannabidiol, the potency of an average purified red oil and of a highly active portion of red oil obtained from it by extraordinarily careful fractionation. The increased activity of the optically active natural tetrahydrocannabinols is striking. The commercial cannabis fluid extracts are of very low and variable potency.

In Chart IX, the potency of products of questionable purity produced from pulegone and various olivetol homologs, together with their hy-

CHART IX

Pulegone Condensation Products

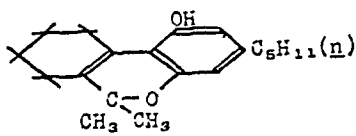
| R = n-alkyl | Potency | |
|-------------|-------------------|------------------|
| | Original products | Reduced products |
| C_3H_7 | below 0.23 | < 0.20 |
| C_4H_9 | $0.25 \pm .10$ | < .15 |
| C_5H_{11} | $.58 \pm .12$ | $.64 \pm 0.10$ |
| C_6H_{13} | $1.22 \pm .12$ | $.78 \pm .22$ |
| C_7H_{15} | $1.15 \pm .15$ | $.83 \pm .17$ |
| C_8H_{17} | $1.37 \pm .25$ | below .25 |
| C_9H_{19} | below .20 | |

drogenated derivatives are shown. The maximum potency appears in the *n*-octyl molecule, and the values for the *n*-heptyl and *n*-octyl derivatives exceed those of the corresponding products synthesized by an unequivocal procedure.

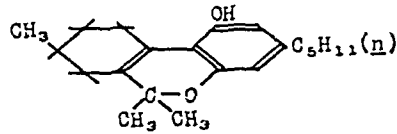
Finally in Chart X, the activities of other analogs are shown. Each has an activity less than that of the molecule possessing methyl groups in the 6,6,9-positions.

Recognizing that the indulgence in marihuana in New York City has constituted a growing problem of major consequence involving psychiatric, medical, legal, sociological and civic aspects, a clinical study was undertaken by a committee appointed by Mayor LaGuardia and supported by funds allotted by several foundations. The primary objectives were the determination of the mental and physical actions of marihuana on the kind of person resorting to its use and the consequent social implications. Dr. Samuel Allentuck directed the clinical studies in a unit of the Welfare Island Hospital and the facts I am presenting have been summarized from his report on the results.

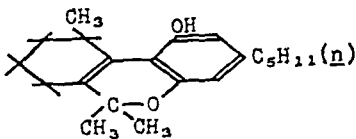
An orientation group, the members of which were subjected to numerous and varied procedures, was used to determine precisely which tests would best lend themselves to the solution of the specific problems. From the results a program was established which consisted in a systematic study of a group of seventy-seven subjects ranging in age from 21 to 45 years and from borderline to superior in intelligence, all of them voluntary recruits from one prison population. About half had used marihuana previously. After a physical, neurological, and psychiatric examination, they were placed in one or more of five categories as to personality types—normal, antisocial, autistic, cyclothymic and epileptic. Each individual before and during the period of action of



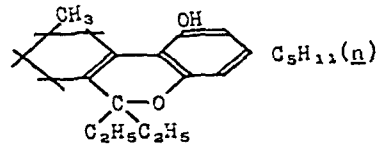
0.126±0.05



0.137±0.01



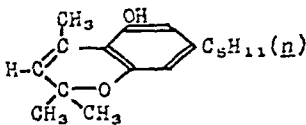
0.25±0.05



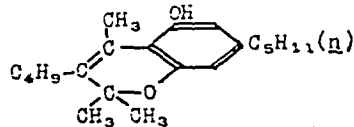
0.12±0.024

(C₃H₇)(C₃H₇)

0.04±0.01



0.033±0.010



0.04±0.01

CHART X

marihuana was interviewed at regular intervals throughout the day by various members of the staff. Possible subjective and objective phenomena resulting from use of the drug were discussed and elaborated upon in detail. Introspective reports were obtained in the absence of the drug, under pseudo-stimulation with placebos and during intoxication with marihuana or allied synthetics; analysis of the data was based on the most frequently mentioned phenomena. The patients were also subjected to periodic tests for blood pressure or pulse changes, pupillary changes, urinalyses, blood chemistries, hematological surveys, basal metabolic rates, electrocardiograms, arterial and venous pressure tracings and vital capacities. In addition, psychological examinations before and during the intoxication periods were carried out, including a wide variety of psychophysical, psychomotor and clinical tests.

The marihuana was supplied in the form of a fluid concentrate which was desolvated and administered in the form of pills. Pure tetrahydrocannabinol was diluted with a little olive oil and placed in gelatin cap-

sules, holding 15 mg. of drug, the equivalent in physiological potency to one pill containing 300 mg. of crude solids from hemp. The 1-hydroxy-3-*n*-amyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran and its 3-*n*-hexyl homolog were administered in a similar manner using the equivalent doses which produced similar activity, namely, 120 mg. per capsule of the former and 60 mg. per capsule of the latter. It is significant that these relative amounts are practically identical with those observed by Loewe for obtaining identical effects in dog-ataxia tests.

The patients were started on two marihuana pills or on equated doses of tetrahydrocannabinol or the two synthetic analogs. The dose was increased by two pills at a time at intervals of two days unless toxic symptoms supervened. At the appearance of toxicity, the patient was returned to the physiological dose and this was increased one pill at a time. Thus the maximum tolerated dose for each individual was determined and at the same time approximately the threshold at which psychotic changes first appeared. Tetrahydrocannabinol and the synthetic compounds dissolved in olive oil were in some cases administered by intramuscular injection. Other clinical tests were made which involved intoxication from smoking marihuana cigarettes.

Barbiturates, cold showers and sweet candies were found to be efficacious in ameliorating any alarming physical or psychotic symptoms which developed following marihuana overdosage.

The detailed results of this carefully planned and executed clinical investigation, the first of its kind on record, must be left to the complete report when it is published. Merely the more significant findings which may prove of maximum value will be presented here. The crude drug in the form of concentrated marihuana extract, tetrahydrocannabinol derived from cannabidiol, and the two purely synthetic compounds, 1-hydroxy-3-*n*-amyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran and the corresponding 3-*n*-hexyl derivative elicited similar clinical and psychiatric phenomena upon the same subjects. The pharmacological action of these drugs somewhat resembles atropine and the psychiatric portrait, alcohol. The effects of marihuana do not vary qualitatively with the route of administration, whether ingested, injected or inhaled. By inhalation, however, they are more prompt in their appearance and disappearance; by ingestion they appear within one-half to one and one-half hours, reach their maximum in from three and one-half to five hours and disappear within seven hours.

The observed physical effects, one or more of which occur in each patient, are (a) elevation of the pulse rate, the increase being directly proportionate to the degree of intoxication; (b) elevation of the blood pressure; this varies with the individual and usually rises in direct proportion to the pulse; (c) injection of the conjunctival blood vessels which varies with the dose; (d) dilation of the pupils and sluggish reaction to light and in accommodation; vision for proximity, distance and color changes slightly; (e) circum oral tremors; tremulousness of the protruded tongue and the extremities; (f) dryness of the oral and pharyngeal mucous membranes; (g) increased frequency with decreased amplitude of thoracic respiratory movements; (h) ataxia; (i) hyperreflexia. The observed psychiatric effects are (a) apprehension and anxiety, (b) euphoria, (c) loquaciousness, (d) lowering of inhibitions, (e) hunger and thirst, (f) feeling of being "high," (g) uncontrollable bursts of laughter or giggles, (h) drowsiness, languor, lassitude and a pleasant feeling of fatigue.

Clinical tests revealed that marihuana produces no significant changes in basal metabolic rates, blood chemistry, hematological picture, liver function, kidney function or cardiac electrical conduction. Marihuana delays somewhat gastric and intestinal motility as gauged by the Carlson apparatus and x-ray studies; it produces definite increase in the frequency of the alpha wave in electroencephalographic recordings thus indicating increased relaxation.

Other observations of a more general character were recorded. Tolerance for marihuana may be produced by repeated administration of subtoxic doses over a prolonged period of time. Thus the same dose elicited progressively fewer and milder symptoms. Marihuana is unlike opium derivatives in that it does not give rise to a biological dependence accompanied by withdrawal symptoms. Neither does it establish a strong craving as exists in tobacco smoking or in alcoholic indulgence. Follow-up of the subjects has failed to establish existence of any craving for the product. Many of the unpleasant physical symptoms previously mentioned appear only as a result of the administration of excessive doses of drug. It is no more of an aphrodisiac than alcohol.

Since all the clinical experiments at Welfare Island were conducted on volunteer prisoners, it was desirable for completeness or perhaps to satisfy my curiosity to obtain some results on subjects in another social class. As a consequence, I have conducted a dozen or more experiments

using as test individuals chemists among whom were two members of the National Academy of Sciences and two high-ranking and very successful industrial chemists. In all cases very small doses, 15 mg. or 30 mg. of tetrahydrocannabinol, were administered about one hour before dinner. Each individual reacted differently with the possible exception of the observed stimulation of the appetite. They all recognized an intoxication which they described as in general like, but in detail different from that induced by alcohol. Thus, one industrial chemist who shows no outward change under the influence of alcohol, reported essentially no effect from 15 mg. except a mild stimulation of his desire for food. A 30 mg.-dose, however, to this same individual had a pronounced effect. Though he noticed no particular craving for food before dinner, as soon as he started eating he became particularly hungry and consumed a very large meal. He felt intoxicated and dissociated from his normal self, had a feeling of heaviness in his head and legs and reported a fogginess which he described as the inability to focus his eyes on more than a single object at a time. Since this man desired to get the effect of distorted time and space which is recorded as a frequent phenomenon associated with the marihuana user, he tried it a third time, taking 45 mg. The result was a ravenous hunger which was not satisfied after eating the equivalent of two hearty meals. A marked hypergeusia was also noted. The same fogginess appeared and heaviness in head and legs. During the conversation which took place among his five associates at the dinner table, he was able to comprehend a question but by the time the answer was given, which was immediately, he couldn't remember the question. In spite of the intoxication with the resulting phenomena, this subject had no difficulty in holding his own and then some in a poker game composed of expert players.

A second industrialist took 15 mg. at 5:00 o'clock in the afternoon and felt the first effects about 6:30 when he lost coördination in his fingers to the extent that he had to stop playing the violin, which he was doing at the time. Shortly thereafter he developed a tremendous appetite which was, if anything, sharpened by eating an enormous dinner and popcorn all through the evening. He had a mild lift about like a cocktail or two on an empty stomach and this and the hunger left about 11:00 o'clock.

A chemistry professor who took 30 mg. had a mildly increased appetite and reported feeling a bit fuzzy during his dinner, which resulted

in difficulty in comprehending what his associates were saying. This was followed by sleepiness and lassitude until the effects of the drug disappeared two hours afterwards. The stimulation was only slight, which paralleled the effect of alcohol upon this man.

A fourth subject of high standing in university circles wrote me in detail concerning his experience. I am quoting from his letter received two days after the experiment.

"This is to report to you on the outcome of my trip conducted under the powerful guidance of the marihuana drops. I would be interested some time to know just how much of what specific material you gave me, but there is no question but that it gave me a most terrific wallop. In brief:

"5:20 P.M. Took two capsules, went for short swim, had a highball and began to feel something beyond the mild glow from the drink about 6:15. By 6:30 felt bouncy in the knees, a little gay and foolish.

"6:00-8:30 P.M. Very much in the fog. Had alternate waves of hilarity and depression. Sat in smoking compartment looking at myself in the mirror, writing notes on the experiment, and feeling very silly and stupid. Would feel the onset of a surge of hilarity and then break into a raucous, rippling laugh. This gayety was not particularly pleasant, however, for throughout I felt wholly dissociated from myself, knew that I was at the mercy of the drug, and greatly resented this lack of control. The feeling was very different from that of being at one or another stage of intoxication, for I looked perfectly clear and normal and I could stand erect without swaying and execute motions with considerable precision. I could not, to my annoyance and as I was well aware, speak or write or think coherently. This bothered me particularly in the waves of depression, when my lips would feel very parched and salty and I would long to break the spell and regain my own consciousness. A very pressing and persistent sensation was that of extreme hunger, but I had sense enough to wait until the laughing spells were under control before going into the diner.

"Here are a few excerpts from the log: '7:20. Not so good; for a few minutes I sat and looked at myself in a silly way. . . . This is *me*. again. I very suddenly snapped out of it and am struggling back to normal. Lips are very dry. Maybe I'm not *quite* out of it. . . . The above is true. I am writing here in a serious vein—but quick, I must write that a minute or two ago I was sitting here in the men's lounge giggling at

myself in the mirror and saying: This stuff does make you feel pretty gay (gay in the neese). Isn't that the damndest thing? [I knew the spelling was wrong but couldn't right it.] . . . 7:42. Yes, snapping out again. I just had a most jubilant laugh and feel another coming along. 7:45, not feeling laughy, feel like hell. This is really awful stuff. . . . 8:03. I feel like a fool. Lips bad. Want water, but I am terribly hungry and wish the experiment were over. I am thinking very much of eating, for I am very hungry. . . . 8:09. Nearly came out of it. It is awful. Helpless, awful feeling. Over, over, when will it be over? When can I eat? . . . 8:13. A fellow just came in to shave. Why now? Why not at this time of the evening EAT. . . . ha, ha. Now I have been silly. Looked silly. . . . ha, ha. Of all places to have this—the train. Bad, bad. Oh I feel like hell, salty lips . . .'

"At 8:30 I devoured an enormous steak dinner with great rapidity and thoroughness, and left no trace of any of the fixings, even though I ordinarily do not eat ripe olives or salad, and although ordinary delicacy would keep me somewhat below the ten crackers I had with my cheese. The food tasted no better or worse than usual, and I had a dissociated feeling that my mouth was a purely mechanical guide for all that came its way, and wondered if mine was not very much the same as the 'appetite' of a cat.

"At 9:00 I felt myself coming out of the spell, and again at 9:15 I felt sane for a minute or two. A little later the sane periods began to predominate, and by 10 P.M. I was back again in control and could sit down and write out the details of a new natural product synthesis.

"Thus ended the trip. I didn't sleep too well or too poorly, and the next morning I felt O.K. and had no hang-over.

"It was an interesting experiment, but I can't write too enthusiastic an endorsement for this drug you fellows are synthesizing. The feeling of well-being would not, in my estimation, equal that from about three highballs, and the penalty seemed to me to be pretty severe. The outstanding impressions were the feeling of detachment from myself and the extreme hunger. Are these both associated with the same part of the molecule? If not, you might hydrogenate out some of the bad effects and thereby obtain a wonderful aperitif."

After the Welfare Island study of every phase of the action of marijuana and the synthetic drugs and after finding no discernible evidence of any permanent deleterious effects, either mental or physical, Dr. Al-

lentuck considered the question of the possible therapeutic value of these substances. The potential availability of pure synthetics of standard potency invites such a study, for hitherto merely hemp extracts were accessible, the clinical activity of which must be determined for each batch of extracted material. Since the outstanding manifestation of the marihuana action is the euphoria which makes its user feel "high," consideration was given to its possible employment as a drug for individuals in various stages of mental depression as cyclothymics, involuntions, reactives, or those with organic conditions in which dysphoria is a dominant factor. The invariable characteristic of the drugs to stimulate the appetite, suggests they might be applicable in psychoneurosis in which a lack of desire for food exists. Many subjects show an alcohol-like picture of intoxication following the use of marihuana. The idea of using these drugs in the treatment of chronic alcoholic addiction was considered and preliminary experiments by Dr. Allentuck on private patients and colleagues were sufficiently encouraging to merit investigation on a larger scale and over a longer period of time.

The euphoria produced by marihuana is in many ways comparable to that achieved by the use of opium derivatives. This suggested the possibility of use in the treatment of opiate derivative addictions to eliminate or ameliorate the withdrawal symptoms commonly experienced during previously attempted so-called "cures." To clarify this question Dr. Allentuck selected a series of cases among drug addicts undergoing treatment. One group of thirteen received 15 mg. of tetrahydrocannabinol orally three times daily at 5:00 A.M., 2:00 P.M. and 10:00 P.M. and a sterile hypodermic injection; another group of fourteen received the same treatment without the sterile injection. Subjective and objective findings were recorded. In general the consensus of subjective opinions favored the new treatment as compared to previous cures and the established routine taken by some of these patients. They felt happier, had a better appetite and wanted to return to activity sooner. These results served as a basis for further study of fifty cases in which quantitative criteria were employed.

Two groups of twenty subjects were selected, one group receiving the tetrahydrocannabinol treatment up to a maximum of ten days and the others receiving none. Members of each group were observed throughout the day. Each morning they were interviewed and any complaints recorded on a chart. Thus an attempt was made to arrive

at a quantitative comparison of the withdrawal symptoms. It was found that the tetrahydrocannabinol treatment was useful in alleviation or elimination of withdrawal symptoms and in diminishing or eliminating the accompanying discomfort which follows cessation of narcotic indulgence. Any withdrawal symptoms under the tetrahydrocannabinol treatment were of a mild character and occurred within the first three or four days following which the patients began to feel much better. The chief complaints were restlessness, headache and dryness of the throat. They had an increased appetite and desire for food which diminished or eliminated such withdrawal symptoms as nausea, diarrhea and perspiration. They felt physically stronger and showed psychomotor activity. The feeling of euphoria produced by the tetrahydrocannabinol helped in rehabilitating the physical condition and in facilitating social reorientation. An outstanding result is a subjective feeling of relaxation. The sleep induced by the drug likewise contributes to the general improvement in the patients' health. These results are in contrast to those from the use of Magendie's solution which produces in the patients contentment for the first three or four days, after which signs of marked discomfort or withdrawal effects appear. The patients after this treatment, upon their discharge were shaky and generally in poor physical condition. These preliminary results with tetrahydrocannabinol justify a more exhaustive study of its possibilities as a means of relieving the withdrawal symptoms in narcotic addicts.

With this brief picture of the results of the coöperative program before you, I may conclude by adding a few remarks about what may be expected from a continuation of the investigations under way. In the chemical field, repeated attempts to synthesize a tetrahydrocannabinol with a double bond in the γ , δ -position have failed. Just recently, however, a new approach has appeared and the results have progressed to the point where I am convinced it is merely a matter of time before the goal is reached. The physiological reaction of this product will allow a conclusion in regard to the relative importance of the position of the double bond in the alicyclic ring and of the optical activity in the tetrahydrocannabinol molecule. Other synthetic molecules of a similar character, which are soluble in aqueous acids or bases and, therefore, perhaps suitable for intravenous injection, are being prepared. It is hoped also to clarify the significant groups and their orientation which induce marihuana activity. Thorough investigation of the constituents

in red oil is necessary to complete the understanding of hemp extracts.

In pharmacology, there is still much to be done in coöperation with the chemist to elucidate in more detail relationship between activity and molecular structure. With pure chemical substances of marihuana activity, it will now be possible to determine experimentally what actions are exerted upon body functions other than those which have hitherto attracted attention. The relationship between the mechanism of ataxia action in the dog and the psychic action in man should be clarified. It has not yet been established that the structural differences between the various marihuana-active substances do not result in a relative prevalence toward ataxia effectiveness by some, psychic effectiveness by others.

In the clinical field, the practical application of these substances must be awaited with the usual necessary patience. The initial experiments of Dr. Allentuck make it appear likely that some use of this interesting drug or its synthetic equivalents will be discovered.

In all phases of this work just completed, the groundwork has been laid so that a wider interest should ensue, and significant contributions may be anticipated in the chemistry, pharmacology and clinical aspects of this class of substances.

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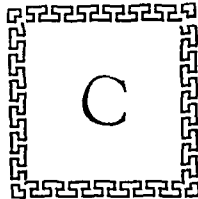
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LYMPHATIC PARTICIPATION IN CUTANEOUS PHENOMENA

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CIRCULATING blood does not come into actual contact with the cells which it nourishes. Instead fluids escape from the blood vessels and, after passing among the cells, return to the blood in part directly, in part after entering a vast system of collecting channels, the lymphatic system. How the fluid moves through the tissues or enters the lymphatics no one knows, but once within these vessels, the lymph, as it is now called, is sieved through the lymph nodes before it is poured back into the blood.

Far too long have the lymphatics been looked upon as a system of passive channels so constituted that fluid from the tissues merely seeps into them and drains away.

It is my purpose to present a wholly different conception: to draw your attention to some active functions of the lymphatic vessels of human and of animal skin. We shall not discuss the physiology of the lymphatic system as a whole, for our chief effort will be spent on the exposition of certain facts recently acquired and not generally appreciated, which show that cutaneous lymphatics in sickness and in health are most active not only in the everyday affairs of the skin but in the processes of immunity and in the defense of the body against infection.

The functions of the lymphatic system have remained largely unknown. Two influences have contributed to our state of ignorance, a lack of suitable methods of study, for the smaller vessels collecting the lymph are so thin-walled as to be invisible during life when examined by the usual techniques, and a lack of interest. The lymphatics were seen by the ancients, but were promptly forgotten and largely through indifference were ignored for nearly two thousand years. Then, in 1622, Aselli made his dramatic rediscovery of the lymphatics.¹ He had just

commenced a vivisection upon a well-fed dog before a small and select group of distinguished citizens of Pavia. He had opened the abdomen, gently put aside the intestines, and there in the mesentery to his amazement he beheld ramifying vessels filled with white fluid—the lymphatics distended with chyle. He described his findings in this way:²

... I suddenly beheld a great number of cords as it were, exceedingly thin and beautifully white, scattered over the whole of the mesentery ... and starting from almost innumerable beginnings. ... Wherefore struck by the novelty of the thing, I stood for some time silent while there came into my mind the various disputes, rich in personal quarrels no less than in words, taking place among anatomists. ... When I gathered my wits together for the sake of the experiment, having laid hold of a very sharp scalpel, I pricked one of these cords ... I had hardly touched it, when I saw a white liquid like milk or cream forthwith gush out. Seeing this, I could hardly restrain my delight, and turning to those who were standing by ... more particularly to Senator Septalius, who was both a member of the great College of the Order of Physicians and, while I am writing this, the Medical Officer of Health, "Eureka" I exclaimed with Archimedes, and at the same time invited them to the interesting spectacle of such an unusual phenomenon. ...

In the two hundred years following Aselli's discovery the early anatomists learned much about the abdominal lymphatics but only a little about the small lymphatics elsewhere. As late as the fourth decade of the 19th century it was generally believed that fluid was carried from the blood vessels to lymphatics by tiny vessels, the "vasa serosa." Belief in such connections was abandoned following Schwann's discovery of the cell, and Virchow³ then suggested that the blood vessels and lymphatics communicated by hollow connective tissue cells. Next, von Recklinghausen⁴ intimated that the smallest lymphatics opened into tissue spaces and that fluid entered through their open ends or through stomata much as rain water might be collected by drain pipes. But subsequent discoveries changed all this. First His⁵ suggested that the lymphatics were closed vessels, a suggestion later to be proven true by the notable work of MacCallum⁶ and of Florence Sabin⁷ who, in 1915, reviewed some of her findings on this subject in a Harvey Lecture.⁸ With this suggestion of His the mechanism of the formation of lymph became a mystery, and a fascinating one, yet to be solved. It was then that lymphatic physiology really began, for speculation and experiment

soon led to the two schools of Ludwig and Heidenhain, the one believing that lymph was formed by filtration, the other that it was secreted into the lymphatic capillaries by the cells of the wall. Lymphatic physiology made its greatest forward step under the influence of Starling^{9,10} and other English physiologists working in his time.^{11,12} Their work can be described briefly as the study of lymph itself, its constituents and its chemistry as bearing on its mechanism of formation, a subject that has been actively extended by Weech and his co-workers¹³ and by Drinker and his group in Boston^{14,15} whose work has already been presented before this Society.¹⁶

Until very recently physiologists have contented themselves with collections of lymph from the larger lymphatics and with observations on the changes in the fluid under various conditions. As a result we know much more about what lymph is chemically than we do of how it forms or under what conditions it flows rapidly or slowly or transports substances from one part of the body to another. One technical difficulty has been that when a lymphatic is cannulated the contents are no longer subjected to the hydrostatic conditions present in the intact channel and the resulting flow from a cannula may be altogether different from that which would have occurred if the lymphatic had not been opened. There are other difficulties which are more considerable. Lymph is formed at the periphery and not in the larger vessels, and the formation of lymph can be understood only after more study of the minute vessels. But the ultimate lymphatics are too small to cannulate and, unlike the blood capillaries, they are invisible.

A few years ago Dr. Stephen Hudack and I utilized various vital dyes as an aid in observing the capillary blood circulation in the ears of white mice.¹⁷ It was noted that when extremely superficial intradermal injections of minute amounts of solutions of these dyes were made at the tip of the ear, some of the coloring matter passed into lymphatic capillaries that had been torn or ruptured by the needle. As the dyes employed had no local tissue affinities they were carried along in the lymphatics with the result that the vessels were rendered visible from the tip to the base of the ear. One could see the smallest peripheral lymphatics as they passed through living tissue that was itself untouched and unharmed, and it became possible to test for the first time the reactions of these channels in health and disease. The ear of the mouse is ideal for such studies, for the anesthetized animal can be placed in

plasteline molds, with the ears spread upon porcelain plaques which serve as reflectors, rendering the most minute vessels visible under the microscope.

ACTIVITIES OF LYMPHATICS IN THE EAR OF THE LIVING MOUSE

Fig. 1 shows the ear of a living mouse prepared in the way which has proved best for observational purposes. To render the lymphatics visible in this and in all the experiments in human skin as well as in the skin of animals, a minute puncture wound through the corium was made, under a binocular microscope, with a dissecting needle ground as fine as possible. The needle was then pushed for 2 or 3 mm. parallel to the surface of the skin and just under the epidermis. Into the tunnel so formed was thrust a gauge 30 platinum-iridium needle attached to a syringe, and a minute amount of dye, about $1/200$ of a cc., was expelled with the least possible pressure. The dye promptly entered the lymphatic capillaries which had been torn or ruptured by the dissecting needle and within a few minutes extended along them to the base of the ear. One can see in Fig. 1 that the channels are typical lymphatics as the histologist knows them, irregular anastomosing channels with bulbous dilatations at the valves. If the colored contents of such vessels are pressed toward the periphery with a microspatula, no flow backwards will take place through the valves but instead the channels will rupture as a rule. Changes in the state of the tissues have much to do with the diameter of the lymphatics, which are at times wide, at times narrow. Spontaneous contraction or contractile response of the lymphatics of the ear to drugs or chemicals has not been encountered in our experience.

Evidence of Lymph Flow in the Resting Ear: Preparations like that shown in Fig. 1 have yielded evidence of lymph flow even in the resting ear. Active movement of dye can be seen to occur along the lymphatics of the ear but as it derived from the injected region it could not be taken as indicative of normal flow. However we have frequently observed, where two lymph channels joined, that dye-containing fluid was displaced and swept aside by another stream of clear lymph, itself unseen, deriving from areas remote from the region of injection, that is to say, from tissue untouched, wholly normal, and not edematous. The phenomenon could not have been due to transmission of pressure from the injected area, for recent work by micromethods¹⁸ has shown that

interstitial pressure in the ear is not increased in such regions.

The Permeability of Lymphatic Capillaries: Previous knowledge of the permeability of the lymphatics has been inferential, being based upon comparisons of the blood and of the lymph from channels large enough for cannulation. But now the permeability of the walls of the smallest lymphatics can be tested directly, though it be in a direction opposite to that of normal flow. In a series of systematic studies^{17,19} vital dyes of graded diffusibility, in various concentrations and in different solutes, with and without protein, were introduced into the lymphatics and the rate of dye escape observed. Even the most indiffusible dye we could find, pontamine sky blue, escaped from the lymphatics. In recent work¹⁸ the escape of this dye from lymphatics has been found to be no more rapid than that of T-1824, which is a dye so indiffusible that it is widely used for blood volume determinations.

Figs. 2 and 3 illustrate the characteristics of dye escape. Fig. 2 represents the ear of a living mouse with lymphatics containing 4 per cent pontamine sky blue dissolved in Tyrode's solution. In this photograph, taken 6 minutes after the introduction of the deep blue dye at the tip of the ear, escape has begun, as evidenced by the fuzzy appearance of the borders of the vessels. Fig. 3 shows the same ear 5 minutes later. Color has extended further from the lymphatics owing to the escape of dye and its secondary spread through the tissues. The passage of dye takes place everywhere along the channels.

As was to have been expected, highly diffusible dyes introduced into lymphatic capillaries escaped more rapidly than poorly diffusible ones. The addition of protein to the dye solution delayed its escape. Dye in high concentration escaped more rapidly than in low concentration. Dye dissolved in sodium chloride solution, isotonic with blood, escaped more rapidly from the lymphatics than did that dissolved in Locke's or Tyrode's solutions. Finely divided particulate matter, India ink or Hydrokollag²⁰ failed to escape at all during the periods of our experiments. In short, the lymphatic capillary wall was found to behave like a semi-permeable membrane.

Changes in Permeability of the Lymphatics: Sharp increases in the rate of dye escape followed mild stimulation of the skin, indicating that there had been alterations in the permeability of the vessels. To demonstrate these changes to the best advantage the most indiffusible dye obtainable, pontamine sky blue, in a 21.6 per cent aqueous solution



Fig. 1—Ear of a living anesthetized mouse, photographed by reflected light, 16 minutes after the injection of the standard dye solution described in the text. The plexus of lymphatics, rendered sharply visible by their stained contents, lies in the corium. Other, deeper lymphatics can be dimly seen. But little dye has passed out from the lymphatics though these have been full of stained fluid since the injection was made, 16 minutes before. $\times 5$.

Fig. 2—Ear of a living, anesthetized mouse with the lymphatics containing 4 per cent pontamine sky blue in Tyrode's solution. 6 minutes after injection of the dye, its escape into the tissues from the lymphatics is well under way. $\times 5$.

Fig. 3—The same ear photographed 5 minutes later, that is to say, 11 minutes after injection. The color has extended further from the lymphatics, owing to progressive escape of the dye and its secondary spread in the interstitial spaces. $\times 5$.

Fig. 4—Ear of a living anesthetized mouse photographed 6 minutes after the entry of standard dye solution into the lymphatic capillaries. 10 minutes prior to the injection the ear had been stroked transversely across the middle, as described in the text.

Sharply localized ecchymoses of dye appeared along the line of stroke, although this latter was so weak as not to elicit any reaction of the blood vessels. Under normal conditions no such escape occurs in $\frac{1}{2}$ hour. $\times 5$.

Fig. 5—The under surface of the right ear was warmed at 43.0 – 43.5° C. for 5 minutes. Both ears were then spread on plaques in the usual manner. 10 minutes after the heating, the standard dye solution was introduced into the skin and taken up by the lymphatics. The photograph was taken after a further interval of 10 minutes. It will be seen that dye has escaped profusely all along the lymphatic channels of the heated (right) ear, while only a little has occurred in the control (left) ear. $\times 2$.

Fig. 6—Photograph of the ear of a living anesthetized mouse, injected at the ear margin with the standard dye solution described in the text, 5 hours after a transverse incision had been made in the skin of the upper surface. The dye entered the lymphatics of the injected area and gradually extended along them to escape from their severed ends, filling the wound with blue dye. $\times 5$.

Fig. 7—The result of an intradermal injection of standard dye solution into the margin of a mouse ear, which had been incised 24 hours prior to the injection and photographed 5 minutes after it. The blood vessels and lymphatics had been cut through. Some of the dye reached and entered the incision but most of it was shunted around it as described in the text. The lymphatics were markedly permeable distal to the incision, as indicated by the abundant escape there, and much less so proximally. $\times 5$.

Fig. 8—Lymphatics in the incised ear of a living mouse photographed 5 minutes after an injection of the standard dye solution. The incision was made the day before and is easily seen in the photograph. Three lymphatic channels, lying probably just beneath the incision, have conducted colored fluid past the region of injury into the tissue at the base of the ear. In doing so much dye has escaped into the incision. The increased dye escape distal to the incision, and the escape proximal thereto, are also well shown. $\times 5$.

(isotonic with blood) was diluted to approximately 1 per cent with a mixture consisting of one part of mouse serum and three parts of Tyrode's solution. This yielded for all the experiments dye at a fixed concentration in a vehicle having the probable protein concentration of peripheral lymph. The character of this "standard dye solution," as we will term it, was such that when introduced into the lymphatics by the technique already described no escape of color could be perceived for 12 to 15 minutes, though shortly thereafter a barely perceptible coloration could be seen.

The readiness with which changes in the permeability of lymphatics follow the sort of stimuli that are encountered in everyday life is worthy of comment. For example, Fig. 4 illustrates the effect of a gentle stroke across the ear. In this experiment and many like it, the ear was stroked with the blunt, round handle of a probe, so gently that the skin was not broken or scratched: no reaction was elicited from the blood vessels nor were the latter ruptured. Ten minutes later the standard dye solution was injected at the ear tip and passed, in 2 or 3 minutes, through the lymphatic channels to the ear's base. In another 6 minutes the photograph was taken. The sharply localized ecchymoses of dye, like beads of a rosary, stand out in the line of the stroke. No dye has escaped elsewhere in the ear.

After such a disturbance of the lymphatics the state of increased permeability is maintained for $2\frac{1}{2}$ hours. Very large molecules introduced into the lymphatics in such an experiment as when a hemoglobin solution is injected escape rapidly but particulate matter, India ink or finely divided graphite (Hydrokollag),²⁰ fails to escape. It is plain from this that the physiological barrier of the walls has been broken down temporarily, but not so their anatomical continuity.

Heat Increases the Permeability of Lymphatics: An extraordinary increase of lymphatic permeability results from the action of heat. The ears of anesthetized mice were allowed to rest on the outer surface of a hollow glass bulb shaped to fit the curvature of the ear. Water at any desired temperature could be made to flow through the bulb. Fig. 5 shows the result of such an experiment. The right ear was subjected to temperatures of 43 to 43.5° C. as it lay on the water chamber for 5 minutes. Ten minutes later both ears were injected at the margins, and they were photographed after another 10 minutes. In the unheated control ear almost no dye escaped, whereas the increased permeability of

the lymphatics of the warmed ear is obvious. Exposure to mild sunlight for half an hour brought about an increased dye escape from the lymphatics, while control experiments showed that in ears brought to the same temperature but kept shaded there was no such effect.

Mild irritation by chemical means produced the same phenomena. For example, a single application of xylol to the skin increased lymphatic permeability enormously. Greater degrees of disturbance had proportional results.

The experiments outlined so far carry certain implications. Influences which come within the realm of the normal—sunlight, slight warmth, a stroke which does not break the skin—these greatly but transiently increase lymphatic permeability. Such changes obviously have a meaning for local conditions. Fluid exchange between the blood and tissues is known to be altered by vasodilatation and contraction, alterations in the systemic blood pressure, and so forth. The lymphatics constitute a more passive system, yet much of their usefulness under this or that condition must depend upon the state of permeability of their walls. None of the injuries we have used so far to alter the permeability of the lymphatic wall breaks down the barrier so completely as to permit the immediate escape of particulate matter; yet insofar as the lymphatic is rendered more permeable to fluids by this or that influence, it ceases to be a walled off channel. We have shown that slight stimuli render the lymphatic wall so permeable that even hemoglobin passes it readily. What is true for the huge hemoglobin molecules cannot but hold for those of the plasma proteins.

Lymphatic Participation in the Repair of Incisions: The part played by the lymphatics in the healing of wounds and in the repair of connective tissue injuries has been largely unknown. Descriptions of the processes yield so little mention of lymphatics that one may well ask, do they share in these phenomena at all? To study their relation to the healing of wounds, incisions about 1 cm. long were made in the skin of mouse ears midway between the tip and the base. Some of the incisions were extremely superficial, some deep, the depth being controlled by observations with the binocular microscope. At varying intervals after making the incisions the standard dye solution was injected at the tips of the ears.

First of all it was found that the behavior of the lymphatics severed by incision differed greatly from that of the blood vessels.

Figure 6 shows the results of a typical experiment. Five hours after making an incision deep enough to sever superficial lymphatics and blood vessels dye was introduced into the lymphatics at the tip of the ear. It passed along the channels and escaped at their severed ends into the incision itself, although at this time constriction and spasm of the blood vessels prevented all bleeding. The picture, taken only 5 minutes after the injection, shows that the lymphatics had not only failed to close during the interval of 5 hours but that the channels distal to the incision were far more permeable than normal, as evidenced by dye escape. Intravenous injections of dye in other experiments showed that the blood vessels about the incisions were also more permeable than normal.

When a drop of dye solution was placed in a superficial cut the lymphatics drained away colored fluid to the base of the ear, showing that the channels were still open. These phenomena were not invariable and whether or not they took place seemed to depend upon how dense a fibrin clot had developed in the wound, hindering access to the lymphatics. The fact that severed lymphatic vessels often remain open for considerable periods of time, unlike the blood vessels, and lead away fluids from wounds readily explains the frequency of infection by way of the lymphatics.

In a few experiments, instead of injecting the incised ears, a tiny crystal of dye was pushed, under the guidance of the microscope, into a minute intradermal puncture wound at the periphery of the ear. Within 15 to 20 minutes colored fluid could be seen passing from the severed lymphatic capillaries into the incision. This occurred of course without application of pressure.

In the experiments in which dye was introduced into the tissues, by hand and through a needle, "the least possible pressure" was employed. Very recent work, which cannot be detailed here, shows that the pressure of such an injection is about 6 to 12 cm. of water. The pressure within lymphatic capillaries of a motionless mouse ear was found by micromethods to be 0.7 ± 0.3 cm. of water, but pressures of only 2 to 4 cm. of water will cause a flow of dye into incisions even several hours after they have been made. From a practical point of view, then, the slightest touch on the skin in dressing a mouse wound will produce results like those seen in the photographs. There is good reason to suppose that the same will be found to hold true for man.

In tests made 24 hours after incising the skin, the dye injected at the ear's tip was mostly carried to within about 2 mm. of the incision and then shunted around it. Only a little reached the wound itself, arriving there from the channels skirting either end. Fig. 7 shows the results of such a test. The photograph was taken 5 minutes after an intradermal injection into an ear incised 24 hours before. Both blood vessels and lymphatics had been cut through. The finding portrayed was that generally obtained but in a few instances dye escaped into the wound, and furthermore, entered directly into lymphatics on the other side of it. Intralymphatic pressures of 30 to 40 cm. of water, brought to bear by micromethods,¹⁸ invariably gave such a result. Fig. 8 shows a photograph of an instance. That lymphatic channels distal and proximal to the incision were abnormally permeable to the dye is obvious in both Figs. 7 and 8.

Forty-eight hours after making an incision, dye intradermally injected by hand with the least possible pressure at the ear's tip regularly failed to enter the incised area and was shunted around it. Intralymphatic pressures of 60 to 80 cm. of water were required to force dye into the incision, such pressure probably dislodging fibrinous plugs in the lymphatics. The permeability of the lymphatics proximal to the wounds seemed to have returned to normal, as judged both by the rate of dye escape, and by the speed at which the channels filled with dye became decolorized as new fluid washed it out. On the other hand, intravenous injections of dye 48 hours after making the incisions showed that the blood vessels all about the incised area were still far more permeable than normal. More will be said of this below, after discussing the changes in the lymphatics about burns.

New Formation of Minute Lymphatics in Areas of Repair: Clear evidence was obtained of the new formation of lymphatics in ears studied 7 to 10 days after incision of the skin. Lymphatics at the periphery of the ear, injected in the usual way at this time, led dye solution or India ink into a wealth of small channels in and about the cuts. Frequently the injected fluids passed, in reconstituted channels, directly through the incised areas. Fig. 9 shows the result of an injection of India ink at the margin of the ear 9 days after making an incision deep enough to sever lymphatics and superficial blood vessels. On the left side of the incision several lymphatics are seen carrying ink either directly through the healing incision or just beneath it. The India ink was used for

purposes of photography, to show the outline of the lymphatics unobscured by the escape of dye. The line of the incision lies between the two arrows on the photograph.

The Participation of Lymphatic Capillaries in the Reaction about Burned Areas: Small, sharply localized, standardized first, second and third degree burns of the ears of mice were made by applying to the skin thin-walled glass water chambers through which water circulated at any desired temperature. Local injections of standard dye solution into the lymphatic capillaries of the uninjured tissue at the ear tip resulted in the entrance of the colored fluid into channels which passed directly through the burned areas, or under them, and emerged again in normal tissue at the ear base. The application of heat of 55°C . for 45 seconds to 1 minute produced a mild first degree burn. Fig. 10 shows the result of an experiment in which dye entered the lymphatics 6 minutes after burning the skin in this manner. Only 2 minutes later the picture (Fig. 10) was taken. The fuzzy escape of dye along the lymph channels in this very brief period outlines the area of the burn, indicating a great increase in permeability of the lymphatics. After another 2 minutes a second photograph (Fig. 11) was taken. The speed of dye escape in this short interval is obvious from the spread of color in the tissues. It is to be noted that dye escaped from the channels only in or near the mild burn.

Occasionally dye introduced into the lymphatics at the margin of the ear passed directly through small second or third degree burns if the injection were made not too long after the skin had been injured. The great increase in the permeability of the walls of lymphatics in or near such burns is shown in Fig. 12. In the experiment from which this photograph was taken a punctate third degree burn, the clear area in the picture, was made 3 hours before the injection of dye by applying to the skin for 45 seconds a small water chamber heated to 60°C . The photograph, taken only 3 minutes after the injection, shows the extent to which the lymphatics at the edge of the burn and one traversing it have poured their contents into the injury. In this experiment we employed, as in the previous one, the standard dye solution which escapes visibly in the normal ear only after 12 to 15 minutes.

For 24 to 48 hours the sharply localized second and third degree burns, made in the manner described, remained as ischemic patches on the ears, surrounded by regions of hyperemia and edema. Twenty-four

hours after the formation of a mild burn, dye injected into the lymphatics at the ear margin was mostly carried around the region of injury through extremely permeable channels. The lymphatics leading directly to the burned area seemed to terminate in blunt ends, closed perhaps by heat coagulations or fibrinous clots. Occasionally lymphatics transported dye directly through the burn, and when this happened the color escaped so rapidly that one might doubt the existence of lymphatic walls were it not that India ink or other particulate matter similarly injected did not escape.

By the 2nd day the lymphatics which filled most readily, that is those which skirted the burn, began to show normal permeability again. Dye passing along them was carried away instead of escaping from the walls. The finding was of some interest because at this time the blood vessels about the burn were still far more permeable than normal. Fig. 13 illustrates this fact. It shows a ring of intense color about a burn 2 days old due to the escape of dye from the blood vessels 4 minutes after an intravenous injection. Dye had escaped from the highly permeable blood vessels about the burn and not from vessels elsewhere in the ear. At this time the lymphatics had begun to regain their normal permeability.

In the later stages of the repair of burns the lymphatics showed notably active proliferation within the recovering tissue. An example is shown in Fig. 14. In the experiment providing this photograph perforation had resulted from a localized burn of the ear made 9 days before. Twig-like lymphatic capillaries are visible, growing into the ring of newly formed tissue which is closing the perforation, while the abnormally rich plexus of vessels proximal to the injury signifies the fact that new lymphatic capillaries are not only growing into the new tissue but are all about it.

The observation that lymphatics regenerate is, of course, not new. The phenomenon has been described by Lee²¹ and by Colin²² for the thoracic duct, by Reichert²³ for the lymphatics of the limbs, by Clark and Clark^{24, 25} for those of the rabbit's ear, and by others. For our purposes the point of interest lies chiefly in the enormous number of apparently new vessels which appear in the recovering tissue. This observation, which indicates great activity of the lymphatic system in the processes of healing, has been confirmed by Pullinger and Florey,²⁶ whose work has been cited by Drinker and Yoffey.¹⁴

The implications of these findings are not inconsiderable. It is well

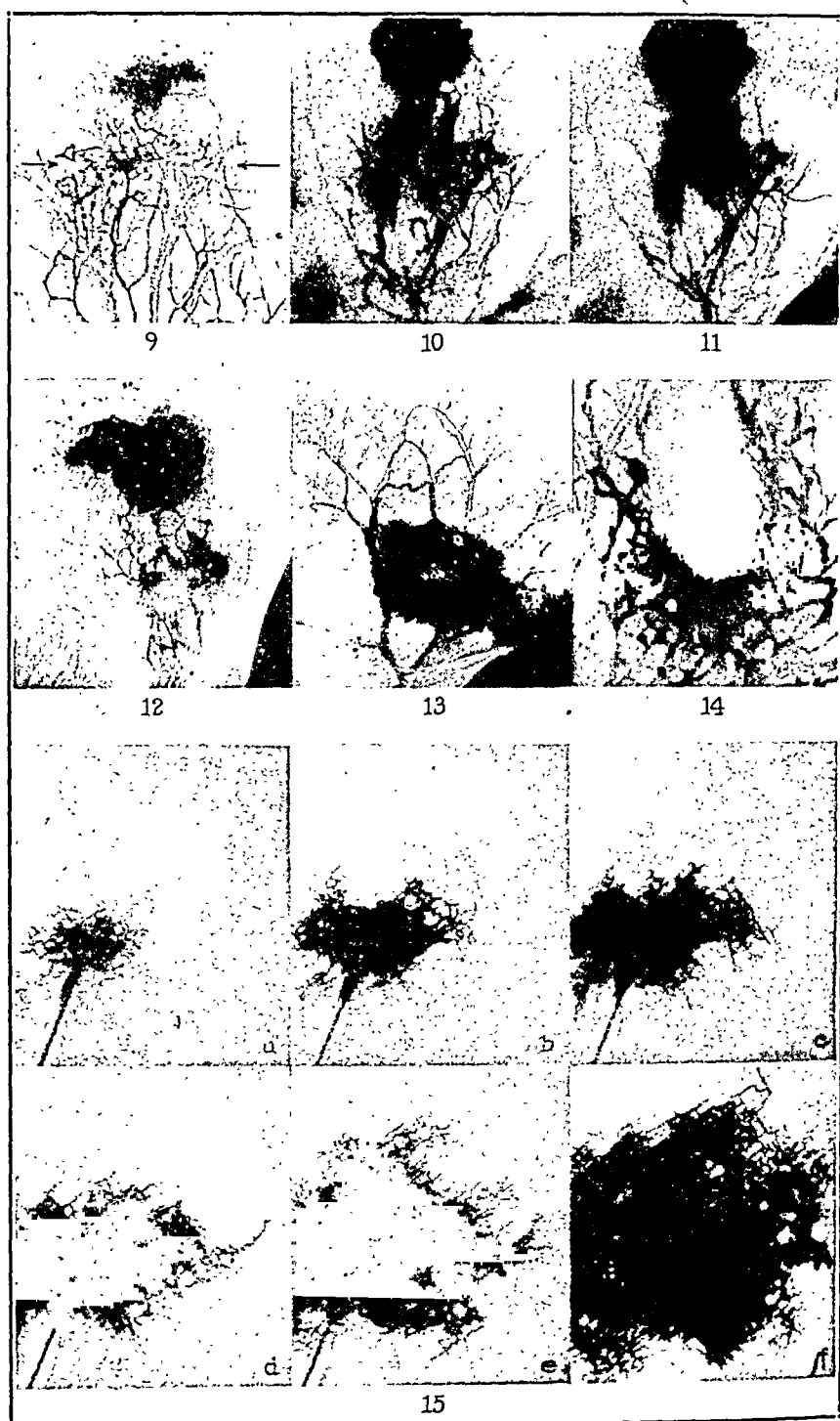


Fig. 9—Demonstration with India ink of the lymphatic plexus about a healing wound. 9 days previously the skin had been incised. In the photograph the incision lies in the line between the two arrows. On the left side of the incision several lymphatics are seen carrying ink either directly through the healing incision or just beneath it. $\times 4$.

Fig. 10—This photograph shows the escape of the standard dye solution into a burned region. 8 minutes prior to taking the photograph a chamber containing water at a temperature of 55° C. was brought into contact, for 40 seconds, with an area midway between the tip and base of the ear. 6 minutes later the dye injection was made near the tip, and 2 minutes later the photograph was taken. The area of dark, fuzzy escape of dye along the lymph channels coincides with the area of the burn. Elsewhere no dye has passed out. $\times 4\frac{1}{2}$.

Fig. 11—The same preparation 2 minutes later, that is to say, 4 minutes after the injection. In unharmed ears standard dye solution does not begin to escape from the lymph channels for 12-15 minutes. $\times 4\frac{1}{2}$.

Fig. 12—A photograph taken 3 minutes after a local injection of standard dye solution at the margin of the ear. 3 hours prior thereto a punctate burn midway between the tip and the base of the ear had been made by heat at 60° C. applied for 45 seconds, as described in the text. Dye passed directly through the burn in one lymphatic and was carried close to it in other channels. The rapid dye escape from the lymphatics in and close to the burned region is shown. $\times 4$.

Fig. 13—A photograph of the ear of a living anesthetized mouse 2 days after a punctate burn had been induced on its upper surface. 4 minutes prior to the photographic exposure the animal received intravenously 0.05 cc. of aqueous isotonic pontamine sky blue solution (21.6 per cent).

The increased permeability of the smaller blood vessels is evidenced by a ring of intense color about the burn, while elsewhere in the ear very little dye has escaped. At the center of the burned area there is some slight diffuse staining. $\times 5$.

Fig. 14—The ear of an anesthetized mouse injected with a suspension of dialyzed India ink in 5 per cent gelatin solution 9 days after a stigmatic burn. The burn had caused a complete perforation of the ear which at the time of the injection was gradually being closed by granulation tissue. Several very small twig-like lymphatics can be seen in the new-formed tissue and about the healing burn there is an abnormally rich plexus of lymphatics, many of which are very small. $\times 12$.

Fig. 15—Successive stages in the distribution of dye during an intradermal injection into the skin of the volar surface of the arm of a living human being. The photographs were selected from a moving picture film and were taken 12, 21, 32, 45, and 65 seconds, and 3 minutes, respectively, after the beginning of the injection which lasted 68 seconds. Note that the injecting needle is seen in the first five photographs but not in the sixth. $\times 2\frac{1}{2}$.

known from the work of many authors that blood vessels in and about regions of injury, mild or severe, are more permeable than normal. Menkin, who has recently reviewed the subject,²⁷ has produced evidence which indicates that substances escaping from the abnormally permeable blood vessels into regions of severe injury and inflammation are fixed there, and furthermore that the lymphatics leading away from these regions may be partially or completely obstructed by fibrin deposits. Such a state of affairs leads to the partial isolation of severely injured regions from the remainder of the body. Our studies show that in and about mild burns, as in and about mild injuries, the permeability of the lymphatics is enormously increased without loss of the anatomical continuity of their walls. The profound alterations in permeability speak for active participation of the lymph system in the changed processes of fluid exchange. Like the blood vessels, the lymphatics respond to injury first by pouring their contents into the region involved, not only into the injured area itself but all about it. As our observations show, the lymphatics regain their normal permeability before the blood vessels do, and through the lymphatics resorption from injured areas seems first to begin. One may suppose that through them the noxious products resulting from injury are carried away and sieved through lymph glands before reaching the body at large.

STUDIES OF THE LYMPHATICS OF LIVING HUMAN SKIN

The physiology of human skin has been written as though blood vessels, nerves, and interstitial fluid alone were involved in its activities. The lymphatics have been almost ignored. To learn what goes on in them the techniques just described were applied to human skin and by their use the lymphatics of living men were rendered visible for the first time.

The injections into human skin were made as already described for the mouse ear save that a more diffusible dye, patent blue V,²⁸ was employed to avoid enduring discoloration of the skin. The six photographs of Fig. 15 illustrate the results of an intradermal dye injection on the volar surface of the forearm of a normal subject. The photographs presented were taken at intervals of approximately 15 seconds after the beginning of the injection which lasted slightly over a minute. The channels rendered visible by the dye lie in the subpapillary layer of the corium and the lymphatic plexus there is far richer than had previously

been supposed. In the past gelatin injecting masses have been usually employed to study them, thicker mixtures which enter only a small fraction of the channels present in the skin. We have found too, as the photographs show, abundant anastomoses, which deserve emphasis because of a further finding, to be described below, that every wound through the human corium tears lymphatics open and allows foreign material to enter them directly. Indeed the lymphatic plexus is so close-meshed that one cannot make an intradermal injection without injecting the lymphatics.

Fig. 16 shows the results of two intradermal injections of dye in a living arm. Pigment, pale because diluted with lymph, is beginning to drain from the injection site into subcutaneous lymphatics and can be seen under the skin as dimly visible colored streamers ascending the arm. The invariable occurrence of such streamers following intradermal injections of dye has suggested that dyes might be used to study changes in cutaneous lymph flow. To test the point they were employed as will now be detailed.

For injections like those photographed in Figs. 15 and 16 nearly 0.1 cc. of an 11 per cent solution of the dye, patent blue V, was employed.²⁸ Though the bulk of fluid introduced was so small, dye drained rapidly away into the deeper subcutaneous trunks. In the experiments to be discussed below far less dye solution was injected, only 0.01 to 0.02 cc. for each test. Further, the concentration of the dye solution was reduced to 1 per cent, which yielded just enough color to be visible in lymphatics under the skin.^{29,30} The decrease in concentration and volume of material injected reduced the amount of pigment to about 1/50 of that previously employed. The resulting streamers formed slowly, requiring about 20 minutes to become 10 to 15 cm. in length. As a result variations in their length and intensity could easily be distinguished.

In Fig. 17 (a-e) natural size photographs of the results of a minute injection of the sort mentioned have been reproduced. They were taken at intervals of 30 and 45 seconds, 1, 2, and 3 minutes, respectively, after the dye first began to enter the lymphatics. The injection in this instance required only 52 seconds. All the injections to be considered below required less than 1 minute. A greatly reduced photograph of the arm (Fig. 17f) shows a characteristic streamer which developed in the ensuing 20 minutes.

It is to be stressed that following a minute injection of this sort the

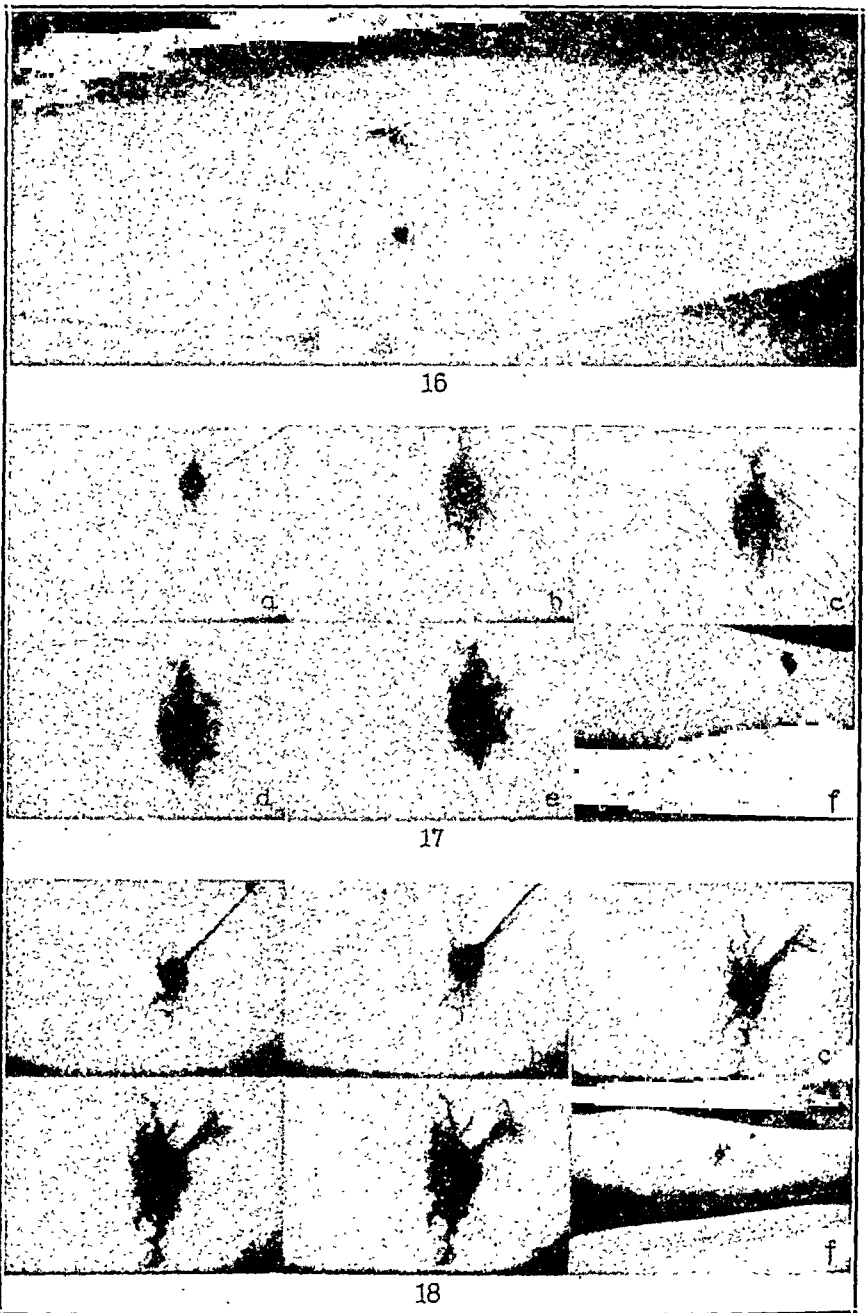


Fig. 16—The aftermath of two intradermal injections of a vital dye, patent blue V, into the skin of the volar surface of the arm. Dye, pale because diluted with lymph, is draining up the arm in subcutaneous lymphatics. $\times \frac{1}{3}$.

Fig. 17 a-e—Natural size photographs of the distribution of dye on intradermal injection into the skin of the volar surface of the forearm. The photographs were taken 30 and 45 seconds, and 1, 2, 3, and 20 minutes after beginning the injection. Fig. 17 f is reduced to $\frac{1}{7}$ natural size and shows a colored streamer extending up the arm from the injected area.

Fig. 18—Results of an intradermal injection of dye into the skin of the volar surface of an arm during a period of venous obstruction, caused as described in the text. The injection was made after pressure had endured for 20 minutes. Fig. 18 a-e was taken at the same time intervals as Fig. 17 a-e. Fig. 18 f, however, shows only part of an intense blue streamer which formed in 2 minutes following the release of the venous obstruction. $\times \frac{1}{7}$.

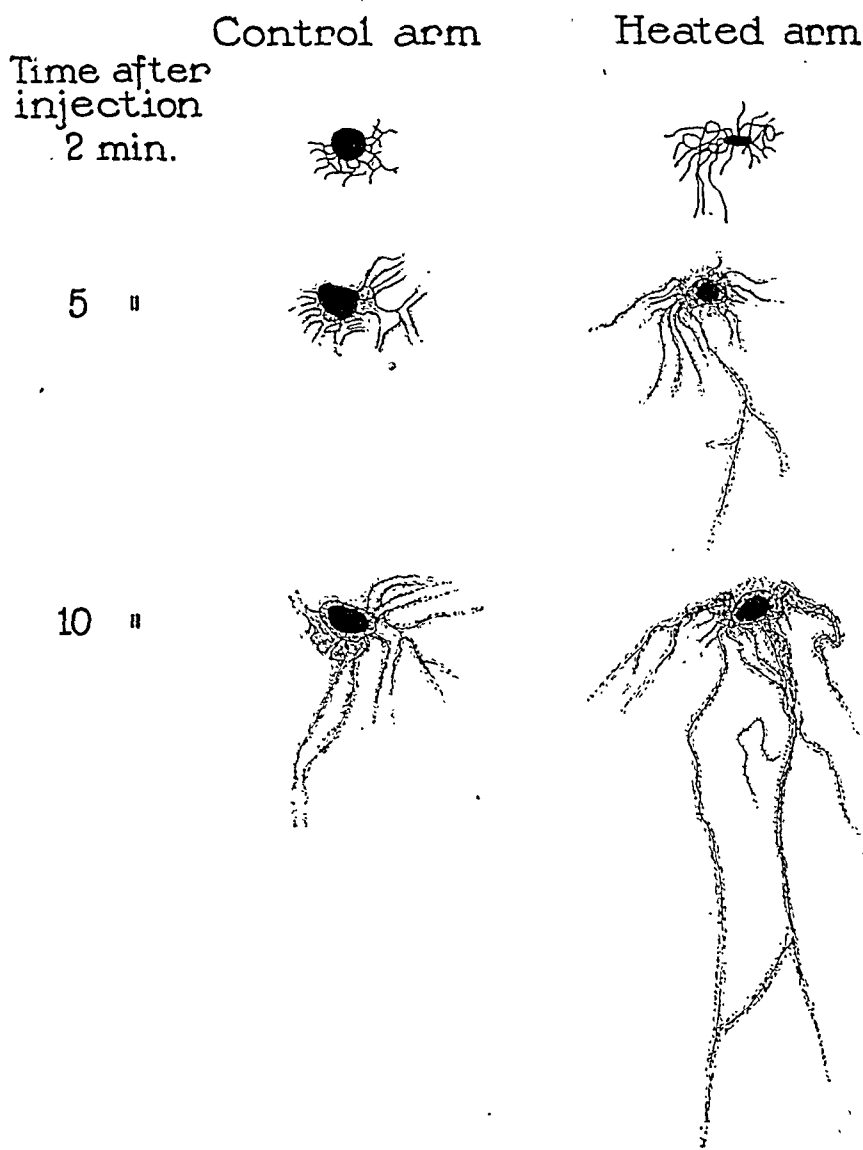
development of a streamer is a very different phenomenon from that obtained when larger amounts of dye are forcibly injected into skin to obtain anatomical preparations of the lymphatics. Under the latter circumstances undiluted dye is actually forced into the lymphatics under great pressure and is not transported by flow along them. In our experiments minute amounts of dye solutions, isotonic with blood, are injected with the least possible pressure into the tissues. From the injected area the solution, diluted by tissue fluids, extends very slowly into superficial lymphatics, there to be still more diluted. Slowly, and only after some minutes, it reaches the lymphatic trunks as dye at the site of the injection is further diluted by tissue fluid, to become lymph. To be sure, some pressure is unavoidably employed in making an injection but, as already mentioned, it is slight indeed, varying from 6 to 12 cm. of water. Recent work has shown that the pressure in the bleb of injected dye is only 4 to 8 cm. of water and falls rapidly to become equal within 4 minutes to the usual interstitial pressure of less than 2.0 cm. of water.

CHANGES IN LYMPH FLOW REFLECTED BY CHANGES IN THE LENGTH AND INTENSITY OF THE COLORED STREAMERS

The Effects of Agents Known to Stimulate or Retard Lymph Flow:

To test whether or not changes in lymph flow in human skin find reflection in changes in the length and intensity of the streamers, use was made of the common knowledge that lymph flow is increased by applications of heat,^{9,15} by massage,^{13,15} by activity,^{31,32} or by hyperemia,³³ and that it is diminished in limbs that are at rest.^{9,13,14}

Constant amounts of standard dye solution were injected into corresponding skin areas of the arms and legs of normal subjects whose limbs were then subjected to one or another of the conditions just mentioned. Tracings of the streamers as they developed were made on strips of celluloid held over the skin. Text-fig. A shows a series of tracings of streamers which developed from two similar injections made at approximately the same time on the volar surface of the resting forearms of a normal subject. One arm remained at room temperature while the other was submerged in warm water at 46-47° C. Both arms were motionless, at the same level below the apex beat of the heart. Both injections were made with the same amount of dye solution, at the same pressure, and the conditions about the injection site were similar. Heat, which is



Text-Fig. A.—The effect of warmth to increase lymph flow. Tracings of two similar intradermal injections of dye in the forearms of the same subject, 2, 5 and 10 minutes after injecting. Dye escape from the lymphatics is indicated by the stippling. Column 1 shows the result in the normal resting arm, column 2 in the arm resting in warm water at 46.0–47.0° C. In the warmed arm streamers developed more rapidly. Natural size.

known to increase lymph flow, increased both the intensity and the length of the streamers. Ten experiments all gave similar results.

When an arm injected in the way described was used to pummel a punching bag, intensely colored streamers developed and reached the shoulder in a minute or two. Massage also brought about the rapid for-

mation of intense streamers, by an actual squeezing of the dye along the channels. Passive movement yielded less pronounced effects than active movement but nevertheless a definite increase in the length and intensity of the streamers was seen. In all our experiments the streamers were shortest and least colored in resting limbs.

The effects of posture were striking. In an arm intradermally injected with dye and held vertically downward at rest, streamer formation was absent; whereas when the same arm was raised vertically above the head and then injected, it was rapid. Streamer formation was absent in the injected lower legs of normal subjects seated quietly with the feet resting on the floor, but conspicuous if, a few minutes later, the injected leg was elevated and propped on a table while the subject remained seated. Streamer formation was still greater if a limb which had been hanging downward was raised and immediately injected.

The lack of streamer formation in the dependent limb is of much interest. It is well known that in the dependent limb fluid collects; the mechanism is charged as it were for lymph formation yet no streamer develops. If a lymphatic is cannulated under these circumstances, lymph flows from the cannula, for the back pressure from the vertical column of lymph above the point of cannulation no longer exists, as in the intact system, to prevent the movement of lymph.

It is to be noted that in the tests on human skin, so far described, the streamers showed great differences under different circumstances although the conditions of injection, that is, amount of dye, concentration, pressure, and the local edema at the site of injection, were the same. Procedures known to increase lymph flow caused an enhancement in the size, number and intensity of the colored streamers developing after injection of small amounts of dye in the skin. In resting limbs, in which presumably lymph flow was least, streamer formation was least.

The Effects of Some Conditions Having a Problematic Influence upon Lymph Flow: With these facts established, we studied next the changes in streamer formation brought about by conditions having an unknown influence upon lymph flow. No streamers ever appeared in the skin of the forearm or lower leg if pressure, even as little as 10 mm. of mercury, was applied to the upper arm or leg by a pneumatic cuff. By contrast the most rapid formation of streamers that we have ever seen occurred in motionless limbs during the reactive hyperemia that

follows release of obstruction to the circulation.

Fig. 18 (*a-e*) shows some photographs of the skin of a forearm injected with dye 20 minutes after bringing about venous obstruction by inflation of a Riva-Rocci cuff to a pressure of 90 mm. of mercury. The photographs were taken at the same time intervals as in Fig. 17. No streamers developed during a further 20 minute period of obstruction. The final photograph, Fig. 18*f*, shows only part of an intense blue streamer which formed in less than 2 minutes after release of the pressure cuff. The streamer at that time reached the shoulder. No streamer so long or intense was ever found at any time after a similar injection in a normal arm.

Fig. 19 *a* and *b* shows the result of an experiment in which several dye injections were made intradermally during a 40 minute period of total circulatory obstruction. During this period no streamers developed. The obstruction was then released and the streamers shown in Fig. 19 *a* appeared in 1½ minutes. Fig. 19 *b* shows them again after a further interval of 1½ minutes. The great increase in intensity is striking. The phenomenon occurs during the intense reactive hyperemia which invariably develops almost immediately after release of the obstruction.

INFLUENCE OF PULSATION OF BLOOD VESSELS ON THE MOVEMENT OF LYMPH IN MOTIONLESS TISSUES

It is noteworthy that streamers representing the movement of colored fluid through the lymphatics can develop with such great rapidity in a motionless limb. How can one account for this? It is well known that massage, muscular movement and other mechanical factors increase lymph flow. But in the resting limb what mechanical forces are present? Can it be that the pulsation of blood vessels acts to further the flow? To test the point, we resorted, together with Robert Parsons,^{34, 35} to experiments on the rabbit's ear.

In preliminary tests minute amounts of dye solutions were injected intradermally at the tips of the ears of many rabbits. Colored streamers appeared like those in human skin, reaching to the base of the motionless ear in about 15 minutes. In each experiment many lymphatic capillaries and small lymphatics, which contained color 10 to 15 minutes after the injection, became cleared a few minutes later. Often these channels lay far toward the base of the ear, too far away from the injected area to be subject to influence by any local edema there. Clearly lymph flowed

into those channels from regions of the ear that were untouched and, in sweeping out the colored fluid already there, gave evidence of lymph flow from areas of motionless tissue. When the ears were warmed to 45° C. they became hyperemic, and under these circumstances the blue streamers reached the base much faster than in the normal ear. Channels containing color a few minutes after the injection were cleared much more rapidly too. That is to say, hyperemia, which is known to increase lymph flow, hastened the rate of streamer movement and the clearance of channels in the rabbit's ear.

The ears of rabbits were next perfused with defibrinated rabbit's blood in such a way that a pulsation simulating the natural could be imparted to the fluid or withheld at will. In the absence of pulsation there was almost no movement of lymph, whereas when pulsation was present, lymph flow, as estimated by the streamer formation, was 15 to 20 times more rapid despite the fact that the "systolic" pressure in the pulsatile perfusions never exceeded the constant pressure of the non-pulsatile perfusions and the volume flow in the former was often but one-seventh that in the latter. Variations in the pressure and flow in these experiments demonstrated clearly that the mechanical effect of the pulse increased the movement of fluid both into and along the lymphatics.^{34,35}

Other Mechanical Forces Favoring Lymph Flow in Motionless Tissues: Micromethods have been used to measure the intralymphatic capillary pressure in the skin of mice and rabbits, as also the pressure required to produce flow in the capillaries and interstitial pressure, often called "tissue pressure," outside the capillary wall. Under normal circumstances the intralymphatic capillary pressure is approximately 0.7 ± 0.3 cm. of water and the pressure required to produce flow is 0.3 to 0.5 cm. of water higher. The interstitial pressure outside the lymphatic capillary wall has never yet been found lower than the pressure required to produce lymph flow. Occasionally the two pressures have been found equal, but in nearly all instances the interstitial pressure has been higher by 0.5 to 1.5 cm. of water. In conditions of inflammation or suddenly forming edema the interstitial pressure may exceed by several centimeters of water the pressure required to produce lymph flow. As a result there exists usually a gradient of pressure tending to force fluid from the tissues into and along the lymphatic capillaries.

The experiments upon the ears of rabbits afforded us our first oppor-

tunity to determine whether streamer movement represents the actual movement of lymph in a lymphatic or whether the streamers are artifacts. The point is of much importance, for physiologists generally regard the lymph flow from motionless limbs as negligible. We have seen that colored streamers in resting human limbs extend 10 to 15 cm. in about 20 minutes. Under the circumstances of our experiments, there is an appreciable movement of colored substances introduced into the lymphatics of the skin of a resting limb and, as we have described, much more movement in a limb moved or subjected to changes in pressure. One may well ask: Do the streamers which develop in normal arms represent the movement of lymph taking place normally or is there an artificial movement caused by local edema at the site of injection?

A way was found to test the point by experiments upon the ears of rabbits. On numerous occasions lymph was collected from one of the large lymphatics at the base of the animal's ear. The flow of lymph in the motionless ear was found much greater than that reported by Henry,³⁶ who collected lymph in a similar manner. In our experiments, after collecting lymph for 1 to 2 hours, an intradermal injection of dye was made in the usual manner at the ear tip. Color appeared in the lymphatics at the tip as usual and passed to the channels at the base of the ear and into the cannula in approximately the same time that it does in normal ears. In most of the experiments, during this period the rate of flow of collected lymph did not change. In the remainder an increase of less than 10 per cent occurred.

In many cases the ear was warmed to 44° C. after lymph had been collected at the ear base for 1 to 2 hours. Dye reached the channels at the base of the ear and entered the cannula in about half the time required in the preceding experiments. The flow of lymph into the cannula increased greatly, the increase in flow being approximately proportional to the increase in the rate of movement of the streamers.

One can conclude that there is slight lymph flow from the skin of bodily regions that are at rest and that the injection of minute amounts of dye, 0.01 to 0.02 cc., as in our experiments, either does not affect the rate of flow or augments that already present by less than 10 per cent. Hence the rate of formation of streamers gives a close indication of the rate of lymph movement from uninjected tissues. In this connection attention should be called to the fact that the volume flow represented by a streamer moving 10 to 15 cm. may be very small because the skin

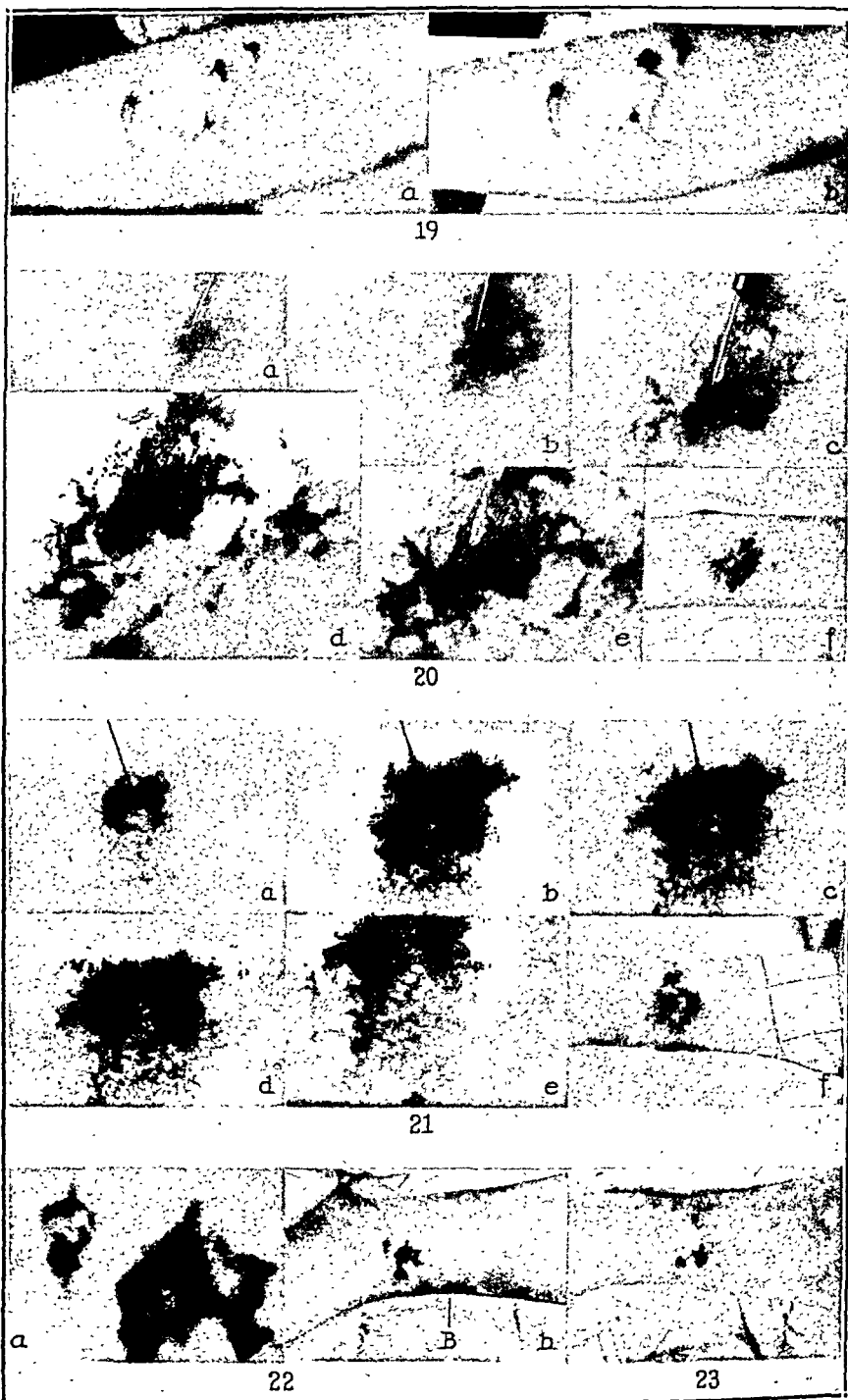
lymphatics, though broad, are flattened and ribbon-like. The point of chief interest to us in this relation is not that a certain volume of lymph in cubic millimeters or cubic centimeters flows through a given channel, but that substances entering a lymphatic through a scratch or puncture can be carried far in a short time.

LYMPHATICS AND LYMPH FLOW IN EDEMATOUS SKIN OF PATIENTS WITH CARDIAC AND RENAL DISEASE

In certain types of cardiac and renal disease fluid collects in the skin with result that edema makes its appearance. Do the lymphatics fail in their function of tissue drainage under these circumstances and add to the abnormality or do they assist in recovery? Since the dye injection technique clearly demonstrates known changes in lymph flow, it was used to answer this question. Tests like those made in normal skin were repeated in the skin of the legs of patients suffering from cardiac decompensation. All were elderly patients with no clinical signs of primary renal disease. Studies were made on each patient while edema increased, when it was stationary, and during resorption.

The dye showed the lymphatic capillaries of the skin to be widely dilated and the intercommunications between the channels extremely rich. The coloring matter when first introduced spread further along the lymphatics and escaped from them more readily than from those of normal skin. Yet no evidence of lymph flow was obtained in any of the tests, streamer formation being totally absent. At the periphery of the injected regions there was abrupt paling, obviously from dilution of the dye in the lymphatics by the copious lymph already present in the channels. Even in tense, distended skin of dropsical patients the lymphatics were widely open but they were full of stagnant lymph. We have reported the dilatation of lymphatics in the edematous ears of mice¹⁹ and Pullinger and Florey²⁶ later described and pictured the phenomenon.

Fig. 20 (*a-f*) shows the appearance of lymphatic capillaries in the edematous leg of a cardiac patient while edema was on the increase. It is typical. The photographs were taken 10, 15, 25 seconds and approximately 1, 3, and 20 minutes, respectively, after beginning the injection. The last photograph, Fig. 20 *f*, shows the extent to which dye had spread in the lymphatics in 20 minutes. Yet there were no colored streamers. Several weeks later the state of affairs in the same patient



while rapidly losing his edema was similar. This fact is obvious from Fig. 21 (*a-f*), taken at approximately the same time intervals following injection as Fig. 20 (*a-f*). There were still no colored streamers, no evidence of lymph flow.

In many instances of long standing cardiac edema, there appeared during the course of the intradermal injection isolated "islands" of dye-containing superficial lymphatics several centimeters away from where the needle had entered. These "islands" were separated from the immediate area of staining by skin of normal hue (Figs. 22 (*a* and *b*) and 23) and were never seen under normal circumstances. It is plain that some of the injected pigment entered the deeper plexus and passing along this emerged again in the superficial plexus. The "islands" appeared below the site of injection as well as above it or at the side, as shown by the arrows "A" and "B" in Fig. 22 *b*.

No matter how much the lymphatic channels were dilated in cases of cardiac edema, we never observed the formation of colored streamers. There was no evidence of lymph flow, yet the fact that the lymphatics

Fig. 19 *a-b*—Streamers developing $1\frac{1}{2}$ and 3 minutes, respectively, following the release of total circulatory obstruction as described in the text. $\times 1/5$.

Fig. 20—Spread of dye in the edematous skin of the ankle of a patient suffering from cardiac insufficiency. The natural size photographs were taken at 10, 15, and 25 seconds, respectively, after beginning the injection, which lasted only 37 seconds. Fig. 20 *d*, composed of parts of four overlapping photographs taken at 10 second intervals from $\frac{3}{4}$ of a minute to $1\frac{1}{4}$ minutes after beginning the injection, shows the size of the injected area. The lymphatic capillaries are seen to be widely dilated and dye escape from them has been rapid. Fig. 20 *f*, taken 20 minutes later, and reduced to $1/10$ natural size, shows the large area then covered by the injection and the absence of deep streamers of dye.

Fig. 21—Results of a dye injection into the ankle of the same patient several weeks later when he was rapidly losing edema. The photographs were taken after intervals of 18, 25, 35, and 55 seconds, and 2 minutes 20 seconds and 20 minutes from the beginning of the injection, which lasted 50 seconds. Again no colored streamers can be seen. The magnifications are similar to those of Fig. 20. The central pale splotches in these and other photographs are high lights caused by dye solution that had escaped on the surface of the skin.

Fig. 22 *a-b*—Result of an intradermal dye injection into the edematous skin of a patient with cardiac edema. The photograph (natural size) was taken $3\frac{1}{2}$ minutes after beginning the injection, which required 48 seconds. Fig. 22 *b* ($1/10$ natural size) was taken 20 minutes after beginning the injection. Islands of dye appeared as described in the text. No streamers were visible.

Fig. 23—The same phenomenon as in Fig. 22 *b* but as it appeared in a different patient $\frac{1}{2}$ hour after injection. $\times 1/10$.

were patent could readily be demonstrated. When a region stained as result of an intradermal injection of dye was massaged, colored streamers promptly appeared. If the skin of the lower leg of a patient with long standing edema was stroked from the injection site toward the periphery, a retrograde passage of dye took place along the superficial lymphatics. The phenomenon was never seen in normal man, nor did it occur in the patient a few days after the edema had been reduced by therapeutic measures. It was plainly indicative of a valvular incompetence of the lymphatics, a state of affairs which would also explain the appearance of "islands" of dye.

The stagnation of lymph in the edematous skin of the cardiac patients is not easily explained. In cardiac incompetence the venous pressure is generally greater than normal. Can the higher pressure in the veins at the point where thoracic duct lymph enters the blood be transmitted to the peripheral lymphatics and account for the stasis of lymph? Four tests were made on this point. Patients with cardiac failure and edema of the ankles and legs but not of the arms were so placed in bed that the wrists and ankles lay at the same level. In this position the effects of high venous pressure at the openings of the thoracic duct, acting to exert back pressure in the lymphatics, must have been the same in the channels draining both the upper and lower limbs. Nevertheless dye injections in the non-edematous arms resulted in the development of colored streamers with the rapidity and intensity seen in normal subjects, whereas dye introduced into the skin of the ankles gave rise to no streamers in the edematous legs. Lymph flow in the arms appeared to be normal whereas in the legs it was absent, a finding which would appear to rule out decisively the influence of back pressure to account for the stasis of lymph.

In contrast to the stagnation of lymph which obtains in the edematous legs of cardiac patients, there was found to be an increased lymph flow in the skin of patients with edema accompanying nephritis attended by a lowering of the plasma protein concentration. The patients were studied during periods of edema increase and diuresis. During the formation of edema there was in all of them a streamer formation, slightly greater than that observed in normal legs; and in all the onset of diuresis was accompanied by an extraordinary and intense streamer formation.

The following is a typical instance. A patient had been injected repeatedly over a period of weeks during which his edema slowly in-

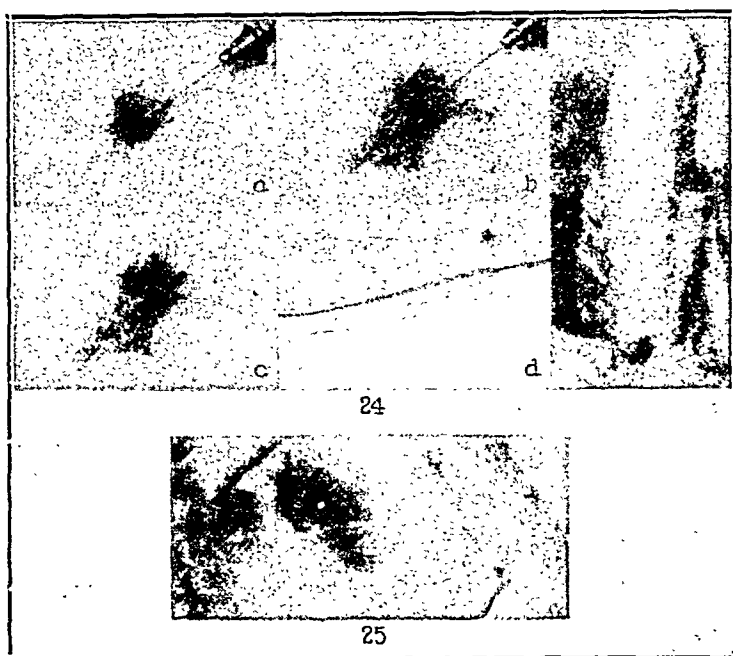


Fig. 24 *a-c*—Results of an intradermal dye injection in an edematous, nephritic patient during a period of diuresis. The injection required 55 seconds. Photographs *a*, *b* and *c* (natural size) were taken 17 and 51 seconds, and 1½ minutes, respectively, after beginning the injection. Fig. 24 *d* (1/12 natural size) and 24 *e* (1/11 natural size) were taken 15-18 minutes after the injection and show the intensity of the colored streamers, which by this time had extended above the knee.

Fig. 25—The displacement of dye-stained interstitial fluid by the intracutaneous pressure of a developing wheal. For details of the demonstration see the text. The wheal, which was evoked by a firm stroke, can be seen as a pale band lying transversely across the picture. Natural size.

creased. In the first few weeks the appearance of the lymphatics differed but little from normal and no photographs need be shown. As edema increased the lymphatic capillaries became wider than in normal legs, though not as wide as in patients with advanced cardiac edema. Fig. 24 *a*, *b* and *c* shows the appearance of the lymphatic capillaries at the height of his edema. By chance the patient had been injected upon the day that spontaneous diuresis commenced. Streamers formed within 3 to 4 minutes after the injection, which were far longer than any we had seen in normal legs even half an hour afterwards. Within 28 minutes intensely colored streamers extended from the ankle to Poupart's liga-

ment. Fig 24 *d* and *e* shows them 15 to 18 minutes after beginning the injection (which lasted only 55 seconds). In many other patients injected during diuresis, even more pronounced and more rapid streamer formation occurred. Such findings have never been obtained in normal skin.

From all this it seems certain that in heart disease the lymphatics fail in their function of fluid transport, adding to the edema. In nephritis on the other hand the lymphatics aid in the removal of the accumulated fluid.

HUMAN SKIN LYMPHATICS AND THE DEFENSE OF THE BODY AGAINST INJURY AND INFLAMMATION

We have studied, together with Hudack,²⁸ the fate of substances entering the lymphatics of human skin in regions of injury and inflammation, repeating many of the experiments made upon the mouse ear and adding new ones.

Permeability studies of lymphatic capillaries of living human skin showed that their walls behaved like semi-permeable membranes, as in the case of the mouse. Highly diffusible dyes passed through their walls more rapidly than poorly diffusible ones. An increase of the concentration of injected dye enhanced its passage through the lymphatic capillary wall but the addition of serum retarded it. In many experiments done under a binocular microscope, scratches were made with a fine sterile dissecting needle, so superficially that only the epithelium was removed, without tearing of skin venules or capillary tufts and without bleeding. Crystals of dyes of graded diffusibility were allowed to dissolve in the fluid transudate into these scratches. Soon the coloring matter appeared in the lymphatics draining the scratched region. The highly diffusible dyes passed into the lymphatics more rapidly than did the indiffusible ones. These findings showed not only that the lymphatic capillary wall behaved like a semi-permeable membrane but it served to test the permeability of the lymphatic capillary wall in the direction which interstitial fluid naturally takes to enter the lymph stream. Further, the experiments demonstrated how readily substances enter the lymphatics after injury to the skin.

Mild stimuli, of the sort met with constantly in everyday life, such as a stroke with a blunt instrument too slight to abrade the skin surface, exposure to heat of 53° C. for one minute, or to ultraviolet light, in-

crease the permeability of the lymphatic capillary wall, as evidenced by a more rapid escape of dye from the channels.

Sharply localized burns were made in human skin either by ultraviolet radiation or by heat. Lymphatic capillaries outside the burned areas were injected and carried colored fluid into the regions of injury. The lymphatics in the latter let dye through into the interstitial tissue far more readily than did those of normal skin.

Skin Lymphatics during Wheal Formation: The behavior of cutaneous lymphatics during the formation of wheals had not hitherto been investigated. If human skin which responds to stroking by wheal formation is submitted to a whealing stroke and the lymphatic capillaries of the region are immediately injected, they are found to be abnormally permeable during the latent period of about 2 minutes before the wheal appears. As it develops the lymphatics are emptied of their contents by the pressure of the wheal fluid and being compressed lose their effectiveness as drainage channels. If interstitial fluid already colored by dye is present it is displaced by the fluid which accumulates and forms the wheal. Since the latter remains uncolored, this fluid presumably is derived wholly from the blood.

The displacement of dye-stained interstitial fluid as whealing occurs is illustrated by Fig. 25. Two intradermal injections of an isotonic solution of a highly diffusible dye, patent blue V^{28,37} had been made in the skin 4 hours before the photograph was taken. The introduction of this dye had produced a mild local edema^{37,38} and the edema fluid had become colored with it. The skin was firmly stroked across the resulting colored patches and 3 minutes later the photograph was taken. The wheal appears as a broad pale band along the horizontal line of stroke. On both sides of it there can be made out a dark line of dye-stained fluid displaced by the wheal.

When histamine together with dye solution was injected into the lymphatic capillaries the latter became much more permeable during the period of whealing, as judged by the rapidity of dye escape from the channels. In several experiments histamine was pricked into a region of skin in which lymphatic capillaries had been injected with dye 2 minutes previously. As each wheal developed the pressure at its extending margin squeezed the colored solution along the lymphatics into normal skin beyond. Dye which had escaped into the interstitial tissue was pressed out of the whealing area, with result that the wheal became

surrounded by a darkly colored ring.

Sir Thomas Lewis³⁹ in his studies of the responses of blood vessels of the skin called attention to finger-like extensions of histamine wheals as indicative of a spread of the substance through the lymphatics, and described secondary wheal formation along the course of these vessels as result of its escape. With Hudack we have injected dye into the skin over fully formed but fresh histamine wheals.²⁸ The coloring matter passed into the lymphatics and each finger-like extension or "pseudo-pod," as they have been termed,³⁹ was observed to contain a dye-carrying lymphatic. During regression of the wheal the dye in the lymphatics faded rapidly, being carried away in the lymph stream.

The part played by the lymphatics in the formation and drainage from wheals has been further studied by Abramson and Engel.⁴⁰ On the basis of their findings and ours it is probable that a large histamine wheal forms, "not by diffusion of the histamine but by convection into the lymphatic capillaries and secondary escape into the interstitial tissues." There, part may act upon blood vessels, part may be taken up again by the lymphatics and escape at a new site to renew its activity upon blood vessels.

The Effect of Local Injections of Toxins and Bacterins: The inflammatory reactions of skin form the basis of many immunological tests; for example, Schick and Dick tests and the skin tests for allergy. In skin inflamed by injections of toxins or bacterins²⁸ the lymphatic capillaries become much more permeable than in normal skin. Dye which escapes secondarily into the interstitial spaces is removed in about one-fourth the time required to remove it from normal skin. For the sake of brevity the experiments which show these points will not be detailed here; we can only refer to published work.²⁸ Suffice it to say that these skin reactions cannot be considered as purely local.

Every Intradermal Injection Is in Part a Systemic Injection: That the lymphatics are involved in local infective processes is well known but the fact seems not to have been sufficiently recognized that noxious materials, whether toxic or bacterial, have immediate access to the lymphatics once the primary barrier of the epidermis is broken. If a sterile sharp needle was dipped into a dye solution or a suspension of dye particles and the skin lightly punctured with it, the dye solution or dye particles appeared in the lymphatics close to the puncture. Isotonic vital dye solutions placed upon a superficial scarification of the skin, like that

employed for clinical vaccination, too superficial to elicit bleeding, were taken up by the lymphatics and carried away. If a knife, dipped in a dye solution or a suspension of fine particulate matter, was used to cut the skin superficially, and the cut was then sucked, as one might suck a similar injury in everyday life, the pressure thus exerted upon the skin forced the dye or the particles which had entered the torn lymphatics several centimeters up the channels. The foreign material could not be squeezed back into the cut. The experiments showed that however slight the injury, colored particulate or diffusible matter punctured, scratched or injected into the skin found its way into the regional lymphatics. Further, as we have already described, severed lymphatics may remain open for a long time. As a result of all this the matter of local injection assumes greater importance in the light of the fact that intradermal injections are to a considerable extent intralymphatic; indeed every local injection is in reality a general one.

THE LYMPHATIC SYSTEM AND DEFENSE AGAINST INFECTION

Since small particles of every sort (amongst them bacteria, poisons, viruses) can enter the lymphatics through every scratch or puncture, what is to prevent them from reaching the blood? It has long been known that lymph nodes act as filters for bacteria entering the lymph stream, but it is also known that they are highly imperfect filters. The possibility suggested itself that the nodes might do more than act as mere filters, that they might play a part in the formation of antibodies.

A variety of experiments done with Hudack have brought out the fact that lymph nodes nearest the site of an intradermal injection of pathogenic bacteria form antibodies⁴¹ before these appear in any noteworthy amount in the blood. Many other experiments have ruled out the possibility that the antibodies found in the regional lymph nodes had really been formed elsewhere in the body.

Proof of these statements reported at length in earlier papers^{41, 42} need not be detailed again. Here we will merely suggest the way in which one type of experiment was done. Killed cultures of agglutinin-forming bacteria were intradermally injected into one ear of large numbers of mice. Into the other ears of the mice Schick test toxin was injected. Daily thereafter, for some while, the serum, extracts from the cervical nodes of both sides, of nodes elsewhere in the body, of the liver, and of the spleen were tested for agglutinin content. After several days agglutinins

appeared first, in high concentration, in the extracts of the cervical nodes draining the ears injected with the agglutinin-forming bacteria. They were present too in the blood, in traces, but they were absent from the extract of the lymph nodes draining the ears injected with the Schick toxin and from the extracts of the other tissues. As the ears and the cervical lymph nodes on both sides were inflamed to the same extent, agglutinins formed elsewhere in the body and present in the blood would have had equal opportunity to be taken up by the cervical nodes of both sides, but they appeared only in the nodes of one side, that injected with the agglutinin-forming bacteria.

Each day the agglutinin content increased in the extracts of the nodes from the side injected with the agglutinin-forming bacteria and in the blood too, but not until a week later did they appear in the extracts of tissues taken elsewhere from the body.

Experiments of the same type, but made upon rabbits, were next undertaken with John G. Kidd⁴² to learn whether the substances which neutralize viruses are also formed in the lymph nodes. It was found that the lymph nodes nearest to the site of invasion form the first antiviral substances neutralizing the virus.

SUMMARY

The experiments here described provide a new conception of the lymphatic system. The lymphatics are very different vessels and far more important than had previously been supposed. They have been considered mere passive collecting channels and rather sparse at that, a view that came to be held because they are not rendered visible by ordinary means. Actually the lymphatics are so abundant in skin that the latter can nowhere be entered forcibly without tearing them, and further, when torn, they remain open. Flow in the smaller lymphatics, even in motionless tissues, is generally far more rapid than has previously been thought and forces have been found to account for it. The transport of foreign substances by way of the lymph is much more rapid than the volume of lymph flow would lead one to suspect, for often the channels are flat and ribbon-like and as result the flow of a very small amount of lymph may carry the foreign materials far through the channels.

The lymphatic capillaries possess walls that respond with remarkable rapidity to highly various stimuli and they are channels which take part

actively in the processes of fluid exchange. Influences that come within the realm of the normal—sunlight, slight warmth, a stroke that does not break the skin—all increase lymphatic permeability. Much of the usefulness of the lymphatics under this or that condition depends upon how permeable their walls are at the time. While they never become so permeable as to permit the immediate passage of particulate matter, nevertheless, at times, they cease to be walled off channels so far as physiological events are concerned.

About injuries and mild burns the permeability of the lymphatics increases enormously without actual loss of the anatomical continuity of their walls. Like the blood vessels, dye-containing lymphatics respond to injury by pouring coloring matter into the region of injury and all about it too. Of greater interest is the fact that the lymphatics regain their normal permeability earlier than the blood vessels do, and hence one may infer that through these channels the noxious products are first drained away and carried to the lymph nodes before reaching the body. Unlike the blood vessels the lymphatics may remain open long after they have been severed, and infectious agents can spread far through the body along their pathways.

The role of the cutaneous lymphatics in edema is of interest. In cardiac edema, perhaps because of extreme dilatation of the channels which renders their valves incompetent, the lymphatics fail in their function of fluid drainage, and so add to the disability. On the other hand, in the edema accompanying nephritis, the cutaneous lymphatics aid in the drainage of fluid from the skin and during the periods of diuresis there is an extraordinarily rapid lymph flow.

Finally, it is most noteworthy that every scratch and puncture, every injury that breaks the continuity of the skin, introduces foreign substances directly into the lymphatics. Every local injection is in reality a general one and as result of lymphatic drainage the regional lymph nodes play their part as the first line of defense, for in the nodes antibodies are first formed against both bacteria and viruses.

From all this it follows that what happens in the skin assumes greater importance now that it is apparent that injections into the skin are really injections into the lymphatic system and that the immunity against disease, conferred by preventative injections, even the reaction to the injection itself, is not merely a skin phenomenon but a generalized activity of the lymphatic system.

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DEATHS OF FELLOWS

ALTMAN, EMIL: 378 West End Avenue, New York City; born in Hungary, June 13, 1873; died in New York City September 11, 1942; graduated in medicine from the Columbia University College of Physicians and Surgeons, New York, in 1895; elected a Fellow of the Academy May 5, 1921.

Dr. Altman was chief medical examiner of the Medical Board of the Board of Education from 1924 to 1941, having joined the Medical Board in 1919, after serving on the school board from 1896 to 1914. He was consulting neuropsychiatrist to the Beth Israel Hospital, a Fellow of the American Medical Association, a member of the American Psychiatric Association, and a member of the State and County Medical Societies.

BROWN, WADE HAMPTON: Princeton, New Jersey; born in Sparta, Georgia, October 18, 1878; died at Rice Lake, Wisconsin, August 4, 1942; graduated in medicine from Johns Hopkins University School of Medicine, Baltimore, in 1907; elected a Fellow of the Academy, January 7, 1932.

Dr. Brown was instructor of pathology

at the University of Virginia, 1907 to 1908; instructor of pathology from 1908 to 1910 and assistant professor from 1910 to 1911 at the University of Wisconsin, Madison; and professor of pathology at the University of North Carolina, Chapel Hill, from 1911 to 1913. That same year he joined the Rockefeller Institute for Medical Research, serving there as an associate member from 1914 to 1922, when he became a member of the scientific staff for medical research. He was a member of the Association of American Physicians, American Association of Pathologists and Bacteriologists, the American Society for Experimental Pathology, the Society for Experimental Biology and Medicine, the American Society for Pharmacology and Experimental Therapeutics, and the American Association for the Advancement of Science.

Dr. Brown was the contributor of more than seventy-five papers to medical journals. He specialized in the study of biology of syphilitic infections, and constitutional factors and physical environment in relation to heredity and disease.

FRAUENTHAL, HERMAN CLAY: 161 West 86 Street, New York City; born in Wilkes-Barre, Pennsylvania, September 15, 1866; died in New York City, August 23, 1942; graduated in medicine from Bellevue Hospital Medical College of New York City in 1897; elected a Fellow of the Academy October 6, 1904.

Dr. Frauenthal was one of the founders and consulting orthopedic surgeons to the Hospital for Joint Diseases, a Fellow of the American Medical Association, and a member of the State and County Medical Societies.

GEYELIN, HENRY RAWLE: 33 East 68 Street, New York City; born in Villa Nova, Pennsylvania, May 12, 1884; died in New York City, September 7, 1942; graduated in medicine from the University of Pennsylvania, School of Medicine, in 1909; elected a Fellow of the Academy January 3, 1929.

Dr. Geyelin was instructor of clinical pathology at the Columbia University College of Physicians and Surgeons from 1913 to 1916, associate in clinical pathology, 1916-1917, associate in medicine from 1917 to 1921, and since then assistant clinical professor of medicine; since 1921 he was associate attending physician at the Presbyterian Hospital, where he was formerly a Blumenthal fellow in medicine and assistant visiting physician; chief of the medical clinic of the Vanderbilt Clinic, 1918-1919; consulting physician to the Babies Hospital from 1923 to 1928, visiting physician from 1928 to 1932 and since 1933 associate attending physician; consultant specialist in diseases of metabolism at the U. S. Veterans' Hospital No. 81 from 1924 to 1933; and

attending physician and a member of the medical board of the Doctors Hospital since 1929. He was a diplomate of the American Board of Internal Medicine, a member of the American Association for the Advancement of Science, the Society for Experimental Biology and Medicine, the Association of American Physicians, the American Clinical and Climatological Association, the American Society of Clinical Investigation and the Harvey Society, a Fellow of the American Medical Association, a Fellow of the American College of Physicians, and a member of the State and County Medical Societies.

TAYLOR, FIELDING LEWIS: 950 Fifth Avenue, New York City; born in Martinsville, Virginia, May 24, 1868; died in New York City, June 22, 1942; graduated in medicine from the University of Virginia, Department of Medicine, Charlottesville, in 1891; elected a Fellow of the Academy June 6, 1901.

Dr. Taylor was formerly an associate in medicine at the Cornell University Medical College and on the staff of the City Hospital and the Hudson Street Hospital. For many years he was consulting syphilologist to the New York Hospital. He was a Fellow of the American Medical Association and a member of the State and County Medical Societies.

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AT 4:30 O'CLOCK

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1942

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DAVID P. BARR, *Professor of Medicine, Cornell Univ. Medical College.*
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- November 20: The surgical treatment of circulatory disorders in the lower extremities, including diabetic gangrene—GERALD H. PRATT, *Assistant Clinical Professor of Surgery, New York Post-Graduate Medical School, Columbia University.*
- December 4: The role of artificial insemination in treating human sterility—
ALAN F. GUTTMACHER, *Associate Professor of Obstetrics, Johns Hopkins Medical School, Baltimore.*
- December 11: Virus pneumonia—HOBART A. REIMANN, *Professor of Medicine, Jefferson Medical College, Philadelphia.*
- December 18: Peritonitis, conservative treatment — HENRY W. CAVE, *Assistant Clinical Professor of Surgery, College of Physicians and Surgeons, Columbia University.*

1943

- January 8: Present concepts and treatment of sinusitis—RUSSELL C. GROVE, *Associate Otolaryngologist, Roosevelt Hospital.*
- January 15: Shoulder pain and disabilities — DAVID M. BOSWORTH, *Associate Attending Orthopedic Surgeon, St. Luke's Hospital.*
- January 22: Indications and contraindications for the newer anesthetic agents —
MILTON C. PETERSON, *Associate Professor of Anesthesia, New York Post-Graduate Medical School, Columbia University.*
- January 29: Modern treatment of the psychoses—S. BERNARD WORTIS, *Professor of Psychiatry, New York University Medical College.*

[BALANCE OF PROGRAM TO BE PUBLISHED LATER]

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE



DECEMBER, 1942

NEUROPSYCHIATRY IN WAR TIME *

GEORGE A. BLAKESLEE

Director, Neurology and Psychiatry, New York Post-Graduate Hospital

THERE can be no doubt that nervous and mental diseases always have been experienced by members of armed forces in all wars but it is only in very recent wars that a well-organized and specialized neuropsychiatric service was given the opportunity to serve as a component part of the medical department in any army, and have the privilege to examine and treat soldiers ill with nervous and mental diseases.

"It was during the Russo-Japanese War of 1904-1905 that the Russians developed the first army medical service in which mental cases were treated by specialists, both at the front and upon return to home territory. During World War I and just prior to our entrance into the war, the Surgeon General of the United States, having in mind the desirability of being prepared at the earliest possible moment to deal with the new and formidable problem of war neuroses, invited a committee of civilian neuropsychiatrists to Washington for a conference on the subject. It is interesting to note that the three members of the committee were from New York City.

The committee visited the army camps on the Mexican border to

* Read before the Combined Meeting of The New York Neurological Society and Section of Neurology and Psychiatry of The New York Academy of Medicine, October 6, 1942.

study the provisions made in the United States Army, as then constituted, for the diagnosis of, and the care and treatment of soldiers suffering from mental diseases.

A member of the committee visited Canada in quest of information concerning the management of the numerous problems arising out of the presence of mental and nervous disorders among soldiers.

Another member was sent to England to secure first hand, the most recent information as to the British and French methods of dealing with war neuroses in and near the theater of operations, to make observations on these methods, and to confer with medical officers in the British War Office.

The foremost recommendation in this report called for rigid exclusion of all insane, feeble minded, psychopathic, and neuropathic individuals from the forces which were to be sent to France and exposed to the terrific stress of modern warfare. By the adoption of an exclusion policy it was believed that the difficult problem of caring for mental and nervous cases in France would be reduced and military efficiency be increased.

Army regulations made no provisions for neuropsychiatrists and it was also recommended that the psychiatrists and neurologists be medical officers of the army. Soon hundreds of neuropsychiatrists were commissioned and recommendations made as to rank. These officers functioned to exclude the nervous and mentally unfit from military service. They were placed on duty at hospitals, camps, cantonments, posts, ports of embarkation, disciplinary barracks, both in this country and France. With the American Expeditionary Forces they coöperated in connection with combat troops, general and special hospitals, court-martials, classification boards and prisons.”*

At the present time, in World War II, although the Medical Advisory Boards of the Selective Service System continue to function, practically all of the psychiatric examinations are made by psychiatrists of the Army Induction Boards, and frequently the final decisions made on registrants is rendered by the regular army, particularly by the qualifying officers in the determining board.

Neuropsychiatrists are assigned in the various camps in the United States, but I am not qualified at the present time, to state to what units or organizations neuropsychiatrists have been assigned in the American

* From *The Medical Department of the United States Army in the World War*, Volume X.

Expeditionary Forces. I am of the impression that the neuropsychiatrists assigned to the camps are overburdened whereas the average high school students could probably do the work that physicians are now assigned to do in the Draft Boards.

I have thought that it might be of interest and value to learn of the experiences of some of the neuropsychiatrists who served in World War I, of others who are serving in the present war, and of one who has had much experience as a consultant in a United States Veterans' Hospital. I have communicated with these men and in the following paragraphs present the substance of their responsive letters:

* * * *

Dr. Samuel W. Hamilton was one of the first commissioned neuropsychiatrists who served in the first World War. He writes that it happened to be for him one of those rare occasions when an amateur military man has a chance to express his preference. Not wanting the war to end without having seen something of it, he asked to be sent abroad early, and the order that called him to duty sent him abroad. He thereby missed the benefit of examining the men in the draft, which all of his friends say was a very valuable experience.

The experience at a British hospital, where the severe psychoneuroses were under treatment was valuable. Perhaps it could have been organized to be still more valuable. The only lesson that he could draw was that medical officers are not afraid to work, and that any courses given to them should assume their desire and their capacity to study earnestly the new problems. He wishes that more of our colleagues were in British and Russian hospitals now.

He spent about six months with a division. It was a fine division and the division surgeon was very pleased to have consultants in any specialty assigned to him and was ready to give them a free hand if they wanted to work. Of course they did. It was indeed a valuable experience. A number of the men who had been trained in the camps at home came over later and he could see that they were doing a better job as division psychiatrists than he was. This is another reason for giving our men stiff training at home. Thus far he has not heard that any of our colleagues in this war has been appointed a division psychiatrist, but he hopes that some will have that experience even though the division may be quite different in organization than in the last war. The same kind of men make it up and emotional problems will need the

same kind of attention. It is said that with the present type of warfare the organization of medical work at the front is considerably different. At any rate the need exists and he hopes our Army Medical Corps will meet that need. It may be remembered that the prize essay printed in the magazine *The Military Surgeon* on the future organization of the division left but two specialists in the division—the orthopedist and the psychiatrist. This essay was written by a man who as division surgeon had not been especially friendly to the idea of having a psychiatrist, but had lived to learn.

Late in July 1918 Dr. Hamilton went to an army corps. Historically, Edwin C. Zabriskie and he were the only corps psychiatrists. He bows to Dr. Zabriskie's superior ability in this as in many other matters—Zabriskie served two corps simultaneously and he served only one.

The work was very interesting as one and another division came into the corps. The corps consultant had to get acquainted with the division surgeon and some of his ranking aides and then make sure that the division psychiatrist knew what was expected of him and had a chance to do it. A quite well-intentioned division surgeon might locate the division psychiatrist at such a place that he would miss seeing a large part of the casualties. The corps psychiatrist was not confined entirely to administrative work, for there were corps troops aside from the divisions that came and went, and it was desirable to hunt up these corps troops, discuss matters with their medical officers and develop in them the same attitude toward mental casualties that the division psychiatrist was developing in his organization. The lesson that he would draw is that the army corps should have a psychiatrist. He needs to be very mobile and will have no difficulty in being very busy.

His last important assignment was psychiatrist to the Army of Occupation. The fighting was over now, but there were still psychiatric tasks to do. Since the fighting was over and the period of parades had come, it was necessary to remove from the divisions a considerable number of men who for various reasons could not parade well. Some of them were feeble-minded; they had been fitted into various jobs that they could perform well, but now with regret they were called out and sent home. The division psychiatrist had this task and the army consultant again was responsible for seeing that there was opportunity to do the work rightly. Then there were army troops as well as corps and division troops and the army consultant was responsible for their mental

health. The army had hospitals and in two of them they set up neuropsychiatric units. Their work was studied and steps taken to relieve them of unnecessary obstacles. Arrangements had to be made also to send their patients to the coast under proper supervision. Obviously, every body so large as an army needs a psychiatrist even when it is static and much more so when it is in the field.

* * * *

Dr. Louis Casamajor who served as a hospital consultant in the AEF writes that the old fellows can reminisce about the last war ad nauseam but he cannot see to what good. He sees no benefit in writing to me about the AEF because he says I know more about that than he does. However, he can say something about the BEF.

When The Presbyterian Unit got with the BEF in Etretat no one there ever heard of a neurologist or psychiatrist in a military hospital. He took over a general medical ward and saw what neurological and psychiatric material they had for him on the side. The neurological material was mostly peripheral nerve wounds and there was important work to be done there but not much of it. Psychiatry was practically non-existent.

He remembers, however, an officer with psychiatric problems—a fine chap named Brooks of the Royal Engineers who came down the line with “shell shock.” He was a typical anxiety neurotic who had blown up after three years in the line. Personally he was a fine fellow who had blown up after having been through a high grade variety of Hell. There were a series of psychotherapeutic talks in which the scare factor of his neurosis was shown. After about three weeks he went back to his company, in September 1917. “I got a letter from him in December of that year in which he said he had been able to help a number of men with what he had learned from us. He also remarked in his letter “If this bloody Army knew what it was doing they would have you up here with us instead of back there at the base.” What he meant to say was that he believed that psychiatry was of more value at the front than in the back areas where usually it was too late. He was killed in March 1918.”

* * * *

Dr. Frederick W. Parsons, who was division psychiatrist of the 1st Division, AEF, one of the finest fighting organizations in Europe, feels that it is fitting that neuropsychiatrists today draw on the experiences

of the last war even though the combat conditions are likely to be very different from what were experienced 25 years ago.

About all that can be visualized now is that the neuropsychiatric service will have to be adjusted to what is possible. It is doubtful if psychiatrists with the troops will have stable psychiatric facilities in which to work. In France, until the end was approaching, the war was one of fixed positions, making it possible to have one's facilities stabilized. It became known where help in neuropsychiatric cases was located and what was there provided largely depended on what the higher officers believed was desirable. Sometimes the intention of those who decided what, where and how much seemed largely devoted to thwarting.

One important opportunity for neuropsychiatric services in war time is the position of division psychiatrist. In theory he should promote the mental health of the whole division, now about 15,000 men. He is, in theory again, expected to spot, to treat and stiffen potential crack-ups and to receive first those who have actually broken; to repair the reparable and to evacuate those not likely to recovery speedily.

No reasonable person can expect one man to do all this. Even with the best help from the division surgeon, with the sincerest interest and assistance of the line officers, he can spot only a few, can help only a portion of those reported to him as becoming unfit, and relieve only a small percentage of those who actually collapse.

Under combat conditions a half dozen physicians in an advanced station may evacuate 1,500 casualties a day. The psychiatrist, if there, probably will be doing dressings, giving first aid, and assisting in the transfer to base hospital during every waking moment and the few mattresses on the ground cannot be devoted to the neuropsychiatrically disabled. The result is that with a mass of wounded men, the neuropsychiatric cases take a long ride to the rear, again to come into a crowded hospital with busy physicians first devoting themselves to those with obvious wounds. The physically indisposed and the neuropsychiatric cases come last.

It is fair to assume that similar conditions will be experienced in our troops when actual combat begins. It isn't likely that trench warfare with fixed positions held for months and sometimes years will be repeated. Then, the rear area could be a quiet zone and a base hospital 50 or 60 miles behind the lines was relatively safe. No realistic person

thinks now that the sick and injured will be permitted to convalesce in comfort.

It is likely that the conditions to be met will in no substantial measure approach those of the last war. Even then, without much official support (there were glaring exceptions), the neuropsychiatrists cannot say they met the situation fully and all they now have to do is to repeat the efforts of the last war. It behooves them to admit their failures. We can take comfort by realizing that the surgeons did not save all of their cases and pneumonia victims died under the care of the internists. Today surgeons have a better technique and the internists deal more effectively with pneumonia, and the neuropsychiatrists will do better with their cases if they have a chance to work with them. What opportunities will be afforded? Perhaps better than the last war as things may work out but for that hopeful outlook they do not have much to stand upon. All they can do now is to look back to 1918 and see what lessons may be drawn.

If one were to say that mistakes were made there would be no difference of opinion. When, however, one asks what mistakes were made, there might be a variety of responses. It is judged that many, perhaps all, would agree that there were men in the combat forces who never should have been there, men constitutionally predisposed to a neuropsychiatric calamity. They were bound to break and never should have been exposed to the strain. Substantial agreement would be had to the allegation that the neuropsychiatrists had but little official support from their immediate superiors. There were striking exceptions but many neuropsychiatric officers were merely tolerated. Then, early in the war, successes in the neuropsychiatric field in the AEF were not outstandingly impressive. Later they improved but by that time the end of the war was in sight and that in itself did more for the men than did the professional care which unquestionably was improving.

Dr. Parsons expects that most of us will say that one important mistake was delay in getting specialized care. If a neuropsychiatrically disabled person can lie comfortably in bed in a good base hospital with only the sympathetic care of a regular practitioner for two weeks, he is almost sure to be a total loss to the Army and of not much use to himself or his family. At the end of two weeks he will have consciously or unconsciously justified his presence in the hospital. Then the neuropsychiatrist has a job on his hands as you well know. Conspicuous success was had

in treating neuropsychiatric cases in a few huts within sound of the guns. There, a few hours after a neuropsychiatric upset while in the trenches, surrounded by men likewise disabled, the soldier had neuropsychiatric encouragement, a hot meal, a long sleep, and the next day was better. After a rest of a day or two, a substantial number could go back. All were bucked up by this speedy return and the soldier had not lost face. That lesson should not be forgotten.

So we at least know three mistakes to avoid:

1. The mistake of poor selection.
2. The mistake of official apathy.
3. The mistake of delayed treatment.

The mistake of poor selection, in the main, has been and is being repeated. Our country is large, the psychiatric resources though great are not evenly spread. Admittedly, in large sections there are but few physicians competent to give psychiatric advice. Generally these large areas are thinly settled so that they produce few recruits. The great bulk of our soldier man power comes from the North and Middle Atlantic Seaboard, from the rich centers of the Middle West and the socially minded Pacific Coast. Probably more than 75 per cent of our soldiers could have decent psychiatric screening. For the State of New York the selection is probably the best in the country and this group knows what is left undone. Poor screening at Induction Boards can be partially compensated for by careful weeding during the early weeks of training. Recently a plan was proposed whereby the non-commissioned officers make check marks against neuropsychiatric symptoms expressed in soldier's language, on a card which goes to the psychiatrists. There may be merit in such a plan, for the men themselves know who among their associates needs psychiatric attention. If the line officers encouraged the non-coms, some decent plan might be evolved.

Official apathy prevails and perhaps it is the fault of the neuropsychiatrists. Maybe they over-exaggerate the importance of neuropsychiatry in a war-torn world. It is possible that performance falls short of promise. So far as official apathy is concerned, they comfort themselves by realizing it is not getting worse. The tendencies will be toward a greater appreciation of the need for neuropsychiatric service and if they perform, full recognition will come.

Now, so far as concerns the mistake of delayed treatment of the battle casualties, they can leave that to those who know what the

battle conditions will be and in an Army scattered in four directions these will not be uniform. All they can do now is to hope that facilities will be provided and that the neuropsychiatrists have an opportunity to avoid the hazards of the first few days of neuropsychiatric disability.

* * * *

Dr. A. A. Brill writes that, notwithstanding all that we have been hearing about the increase of neuroses as a result of the war, he fully agrees with Kraepelin, Bleuler, and all the others who maintained that despite the great hardships, the most intensive psychic traumas, as well as brain injuries, there was no increase in the neuroses as a result of the war. It might interest you to hear how he came to this conclusion long before he heard and read what was said by these great psychiatrists.

"In May 1917, some months before we entered the first World War, an English army officer—a case of "shell shock"—came to me for treatment directly from the battlefield. He was accompanied to this country by a friend, who came with him to my office. Following one of the big "drives," the patient was found in an unconscious state under the debris of a building which was demolished by an explosion. Except for a superficial scar on the back of his neck, no organic injuries were found. Yet, for about two weeks he was in a semi-conscious mental state, and when this disappeared, he showed marked tremors, especially in his arms, and general anxiety. After about two months of hospitalization in France and in England, a military medical commission recommended that he take a vacation far from the scene of war, in Canada or in the United States. A member of the commission, a Dr. Russell, suggested that in the event he chose the States he should consult me in New York, I was quite flattered when he told me this, for I was still at an age when one is pleased by recognition from an unknown colleague.

"The patient was born in Scotland and brought up in Australia; he was 43 years old and married. He had been in the British Army for many years before the war, and as far as he knew, he was never neurotically ill. His main symptoms were marked sensitivity to sounds, tremors, and anxiety, which was still in a free floating state, although some of it expressed itself in phobias and in somatopsychic feelings. He was very timid about meeting people, so that for the first two months he spent most of his time in his room, leaving it only for meals and for visits to me. As he had only four months' leave, and

hence, could not be treated by psychoanalysis, I resorted to other psychotherapeutic measures to help him to get back to the front. After about two months' treatment, he showed considerable improvement and, encouraged by me, he put on his uniform and began to move about in the city. One evening in July, my family being out of town, I asked him to dine with me. After a few drinks he spoke more freely than he ever did in my office (for a quick transference nothing is more efficient than a good dinner with a little alcohol). In the midst of his talk he suddenly opened the back of his wristwatch, took a piece of paper out of it, and showing it to me, said, "I carried this with me for years." I was amazed when I read "Dr. A. A. Brill, 55 Central Park West," which was where I once lived. He then explained that a medical friend of his in Australia, who had corresponded with me, often spoke to him about my work, and one day after he had read one of my letters to him, he cut off my address from it and had kept it ever since. I readily recalled my correspondence with this Australian colleague, who was very interested in the problem of schizophrenia. Thus, I suddenly learned that this man had carried my name and address in his watch case for at least a year before 1914, and that he had thought of getting in touch with me long before Dr. Russell had mentioned my name to him. In brief, this patient had been neurotic for many years before the World War, and his friendship with the medico of his regiment was due to the fact that the latter was interested in mental mechanisms.

"After we entered the war, I had occasion to see many patients who were supposed to have become nervous and mentally ill because of their war experiences. In addition, I have been a consultant to the U. S. Veterans' Hospital No. 81 since its establishment, where I have studied numerous cases of war neuroses; all these observations had long convinced me that nobody becomes neurotic or psychotic as a result of hardships sustained in wars.

"Much good and poor stuff has been written about war neuroses since the last World War, the Spanish civil war, and since the beginning of this war, but judging by the selective service classification of 4-F, which seems to epitomize the sum of this knowledge, I must say that the results are poor to say the least. Thus, 4-F excludes every person who has ever had a neurotic or psychotic attack, or who is sexually abnormal. In the latter case the stress is laid on homosexuality. Let us consider the neurotics first. During the last war I observed a great many

psychoneurotics and some psychotics, as it were in action. Some had been under treatment until they entered the armed forces. Of those, some were conscripted and some volunteered. None of them suffered any breakdowns; most of them served with distinction. I can say the same of psychotics, especially of the manic-depressive type. I have in mind two cases—one volunteered while he was in a depression because he welcomed the idea of being killed. The other joined up while in a mild manic state. The former soon got over his depression and went through the war unscathed. The second one, a patient who was also seen by Dr. Floyd Haviland, later boasted to us that he had a wonderful time. As he put it, "It was just as if you went out shooting rabbits." Yet, when I first heard that those patients were in the armed forces, I was frankly worried; I wondered what would happen to them. Since the first World War, I have seen many neurotics and psychotics, who had gone through the war and claimed that they felt better during that time. Accordingly, since we entered this war, I have been guided by the following rule: All those who say that they are afraid to go into the army, or ask me whether they should go or not, I invariably advise against it. For experience has taught me that they cannot maintain themselves where strenuous effort is required. However, I have in mind three exceptions—men who came for treatment because they were afraid, and have joined up after a few months' treatment, and so far, are doing well. All of them have been advanced to commissioned officers. On the other hand, those of my former patients who wished to go, never asked my advice. I discovered it from parents or relatives, or if they called on me, it was to make sure that I would not stand in their way. So far, all of them are doing very well.

"I, therefore, object to the sweeping regulation that anyone who has ever suffered from nervous or mental diseases should *ipso facto* be excluded from the armed forces. Most neurotics make excellent soldiers. I might add that most excellent soldiers are neurotics.

"I feel the same concerning the exclusions of homosexuals from the armed forces. In the first place, it is practically impossible to enforce this regulation. I happen to know that during the last war there were many homosexuals in the armed forces, who were excellent soldiers, and I know that the same situation prevails also in this war. There never was an army or a navy, wherein there were not many homosexuals. An overt homosexual cannot make a normal man into a homosexual.

Anyone who knows the psychology of this sexual anomaly is well aware of this. Moreover, most homos are decent well-behaved individuals, who control their sexuality in the same way as the self-respecting heterosexual. If we had sufficient psychiatrists well-versed also in psychosexuality, there would be no need for classification 4-F."

* * * *

A member of this society, Norman Q. Brill, Major, M.C., who is at the present time Chief of Neuropsychiatric Service, Station Hospital, Fort Bragg, North Carolina, writes that perhaps the most outstanding experience he has had in his military psychiatric experience which now is of sixteen months duration, has been the discovery of the existence of a tremendous psychiatric awareness in field units as well as in hospital organizations, in line officers as well as in doctors. Military medicine seems to have far surpassed civilian practice in the willingness to recognize functional and mental disorders. Major Brill continues:

"This seems to be so different from everything I have read about World War I medicine. Pearce Bailey related how neuropsychiatry interfered with established military routine and order. He told about officers complaining that if specialists did not cease eliminating the unfit, there would be no army left. 'It was felt that training which transformed poor physical specimens into robust fighters could do the same for those who had nervous or mental disorders. Recommendations for rejection or discharge were often waived by line officers. Because the nervous and mentally unfit were greatly embarrassing the American Expeditionary forces, General Pershing had to urgently cable the Chief of Staff that more extensive effort be made to eliminate such men.'

"The situation now appears to be quite changed. Upon arriving at Fort Bragg and reporting for duty, I was ushered into the Surgeon's office and introduced with the remark "Here's a nut picker." This seeming lack of proper respect for a neuropsychiatrist was more than compensated for by a rather wholesome welcome from the General who arranged for me to be put to work promptly. I have not stopped working since.

"At present, we have five neuropsychiatric wards with a bed capacity of approximately 130. This represents a miniature state hospital and neurological institute. Four of the wards are 'closed' and are for psychotic patients. Four other men and myself constitute the neuropsychiatric section. All the men are well-trained and the work is shared

equally. I might add that the oft repeated complaint of men being mis-used and not assigned in their own specialties can receive no support here. Every psychiatrist regularly assigned on the post is practicing psychiatry.

"Nor are we in want for things to do. We are charged with thoroughly working cases up and disposing of them. While medical and surgical cases which require prolonged hospitalization may be transferred to general hospitals (ours is a station hospital of two to three thousand beds), we must dispose of all our patients locally. This means making arrangements with State hospitals, relatives, and veterans' hospitals. Informal staff conferences are held on problem cases and all psychotic patients are examined by a board of officers prior to discharge.

"In addition to the ward work, consultation service which is probably the more important, is rendered. Daily numerous consultation requests are submitted from all the other sections of the hospital. Before the pressure of work became so great, we would see many patients who complained of inability to perform duty because of flat feet. We quickly discovered that their disability was more often of psychogenic origin than of orthopedic origin and jokingly referred to these cases as "flat heads" rather than "flat feet."

"The cases of neurocirculatory asthenia, and there are many, are seen in conjunction with the cardiologist. We have more than our share of psychoneuroses of all varieties and descriptions, and it is interesting that once again the Charcot types of conversion hysteria are making their appearance. Bizarre gaits, hysterical convulsions and paralyses, amnesias, etc., constantly try our patience and skill.

"A majority of the many psychoneurotics and psychotics we are called upon to see, give a history of previous similar disorder prior to induction or enlistment. Their reactions do not appear to be specific for war, and in the relative quiet and peace of a training camp, far removed from the theatre of operations and areas of combat, numerous cases are seen which in World War I were apparently mistakenly called shell shock.

"One has a wonderful opportunity to observe the variations in "adjustment thresholds" of different individuals.

"It is understandable how men, without previous military experience, drawn from every conceivable walk of life, and thrown together and subjected to the same discipline and routine, in making such a

rapid and violent adjustment can break down. Nevertheless, it is interesting to witness the fact that many of these individuals, on questioning, frankly admit that they are no worse for being in the army—that they “have always been that way.”

“We see numerous epileptics who truly arouse our sympathy. So unlike the psychoneurotics, these men almost without exception plead to remain in the army, and as if they had committed some crime, beg for another chance. One cannot help thinking about their sad plight and wishing for some cure for them. The epileptic personality so frequently mentioned, is not in evidence in these men. In between attacks they are good soldiers, conscientious and willing. Unfortunately, but not without reason, they must be discharged.

“Though we have seen a considerable amount, the organic neurologic disorders have been relatively rare. I have already told Dr. Brickner how, over a period of one year, we did not encounter one case of multiple sclerosis. Recently we have seen two or three. I can assure you that they were not overlooked and I hope not misdiagnosed, for I have been on the lookout for them. I doubt if their absence can be completely attributed to careful screening by induction boards, for all do not have expert neurologists and other cases with obvious organic disease of the nervous system have been passed through. For example, we have encountered some soldiers with Parkinsonism, several with hemiparesis and oddly enough, four cases of typical myotonia atrophica. There have been occasional cases of brain tumor, post-traumatic epilepsy, acute meningoencephalitis, etc.

“All this, however, was to be expected. What is unusual is the frequency with which our opinions are asked concerning disposition of patients and reclassification and special assignments of soldiers. It is gratifying to see how our advice is followed.

“Men who have committed serious breaches of behavior are frequently referred from field outfits for psychiatric consultations before charges are pressed—on the assumption that ‘there must be something wrong with them.’ It is this attitude which is encouraging for the future of psychiatry.

“Before a soldier is brought before a court martial, the officer investigating the charges is required to consider the prisoner’s mental status, and observation and study is recommended when indicated.

“Non-medical officers are alert to abnormalities in behavior, mental

retardation and signs of nervousness. We need no publicity agent. All seem only too anxious to utilize the psychiatric facilities which are available. They have learned how much we can help them.

"The Surgeon General has stated that "The Army is in no sense a social service or curative agency. It is to be considered neither a haven of rest for wanderers, nor a corrective school for misfits, n'er-do-wells, feeble-minded persons or chronic offenders . . . men who present behavior problems in the civilian community will certainly present intensified problems in the service." How true this is!

"General Coburn, the Surgeon at Fort Bragg, remarked to me once, how important the psychiatric service was to the army. This indeed represents progress when one considers how in civilian life in some places, psychiatry is still struggling for a place in the sun in the medical world."

* * * *

My own experiences differed somewhat from those of the neuropsychiatrists just read.

On August 11, 1917 when active in civilian practice, orders were received to report immediately to the Medical Officers Training Camp at Fort Benjamin Harrison, Indiana, where specialists and general practitioners were assembled for intensive training.

The training at Benjamin Harrison proved invaluable in later adjustment to army life, in cantonments and in a combat division in the AEF.

Instruction was given in regular army tactics and manoeuvres, the function and duties at the many army hospitals, the actual erection of a tented Field Hospital, and intensive study of the School of the Soldier and the School of the Officer.

After leaving Benjamin Harrison, I reported to Dr. Hutchins who was chief of the neuropsychiatric service in the 81st Division at Columbia, South Carolina. At that time there was an extremely serious epidemic of epidemic cerebrospinal meningitis in camp, and although the disease stands on the borderline between general medicine and neurology, I was placed in charge and told that particular emphasis should be placed on the prevention of its spread. No opportunity was given, nor was there time to study the nervous and mental diseases in camp.

In a few months, upon my request, orders were issued assigning me to St. Elizabeth's Hospital in Washington, to study the nervous and

mental diseases, under the supervision of Dr. William A. White. The training at St. Elizabeth's was invaluable.

Working in Washington, and in close proximity to the Surgeon General's Office, I soon received orders to go abroad and report to Dr. Thomas W. Salmon, Chief Consultant in Neuropsychiatry of the AEF in France, for duty as division psychiatrist of a combat division. Upon reporting to Dr. Salmon at Savenay, France, he said he wished to talk with me and we entered a small room in a barracks, where he spent much time explaining the duties of a division psychiatrist and said that upon reporting to the division surgeon, my welcome might or might not be cordial, but to adhere to his, Dr. Salmon's, instructions.

His instructions were concluded with what seemed to me a psychological end rather than an approach, by stating that at the front I might not receive a scratch or I might have my head blown off.

Rank means much in the army. The division psychiatrist holds the rank of major and upon presenting my orders to the acting division surgeon, who also held the rank of major, the first information he desired was whether he outranked the psychiatrist and upon obtaining the information that he did by two weeks, we carried on quite well for the duration of the war.

The division psychiatrist was placed in charge of the nervous and mental cases in the Field Hospital, but it was soon realized that the greater number of cases were being sent farther to the rear and not to the Field Hospital. In Dr. Salmon's instructions to me, this was one of the conditions he wished stopped.

The division surgeon was consulted and privilege given to circulate in the division and converse with groups of regimental commanders and surgeons, company commanders, top sergeants, and other non-commissioned officers who were always in close contact with the men.

It was explained to these officers that all nervous and mental cases were to be seen by the division psychiatrist either in their units or were to be sent to the Field Hospital for observation and treatment, and none were to be sent to the rear unless so ordered by the division psychiatrist. Splendid coöperation was obtained with the result that over 40 per cent of the men ill with neuroses were returned to their combat units and fought as bravely as the men who had never experienced a neurosis.

Then there was the soldier who had fought hard and long and who

could always be relied upon by his company commander, but who began to eat and sleep poorly, to lose weight, and seemed to have slowed up and become less interested. He was becoming less efficient in his work, and mixed less with his buddies. On examination it was revealed that he was slightly depressed and extremely fatigued.

On one occasion the division psychiatrist collected about 200 of these men and decided to take them out of the division for a two weeks complete rest. He felt that they were the potential or preneurotic cases and soon would become quite fixed neuroses.

There was no room on the neuropsychiatric service in the Field Hospital for this large number of men and they were taken by the psychiatrist in trucks to Neurological Hospital No. 3, several miles to the rear. There was much eyebrow raising by the staff as they witnessed the men jump out of the trucks and await admission to the hospital. They were accepted on my diagnosis of mild depression and fatigability. They received much needed rest in a quiet environment, mild exercise, excellent hot food, and good sleep. In two weeks time, they were back with their companies, refreshed and very grateful because they were again in excellent health.

Many years later, I was criticized by a member of the staff for having loaded the hospital with these non-neuropsychiatric cases, but in my opinion this was practicing preventive medicine in psychiatry at the front.

The Major General commanding the division, had a good insight into the neuropsychiatric problems in a combat force and on one occasion the general sent for the division psychiatrist to report to him personally at headquarters. The general was not entirely satisfied with conditions in certain units in the front lines and suspected that some of the officers were fatigued or nervous. He ordered the division psychiatrist to visit these units and study the conduct and behavior of the officers. He was to mingle, and mess with them, and obtain their opinions regarding the condition of the personnel in the units. Following the observations and examinations, of all things, the psychiatrist was to report in person to the general and dispense with all paper work. As a result of the examinations and report, high ranking officers, many of whom had served in the regular army for many years, were relieved of duty to rest in the S.O.S. This experience greatly impressed the writer, for he had learned that no one seemed immune to a war neurosis.

On another occasion during fierce combat in the Meuse-Argonne Offensive, a division psychiatrist was stationed at a triage or sorting station situated at a cross-roads, where ambulances could receive the wounded and ill and take them to various hospitals for treatment. It was necessary to write the diagnosis and destination on tags attached to the soldiers. The shelling of the cross-roads by enemy artillery was terrific, and this psychiatrist developed a coarse tremor of the hands of the greatest amplitude, both upon intention and at rest. This tremor did not cease until the day's work was over and he returned to the Field Hospital. The division psychiatrist who involuntarily demonstrated this tremor was myself.

The mild psychoses and war neuroses were treated by using persuasion, suggestion, almost constant personal attention, hot food, rest, and sedatives to induce sleep at night.

Many incidents which occurred in the division aided in the treatment and recovery of the neuroses. One in particular was on the day that Sergeant York, a soldier in the division, almost single handed, brought in his string of German prisoners. This remarkable feat rapidly circulated throughout the division, and the division psychiatrist lost no time in using it for therapeutic purposes.

After the armistice was signed, I was sent to Germany with the American Army of Occupation, to serve as Chief of Neuropsychiatric Unit No. 1, Evacuation Hospital, No. 16 at Coblenz. The hospital was new, modern, and had an excellent hydrotherapy department. After many months in fields and forests, I greatly appreciated the bathing facilities but was very conscious of the fact that I was now many miles farther removed from home.

The neuropsychiatric service was organized and directed as in large general hospitals in the United States. The most common psychoneurotic illness seen was a nostalgia with a mild depression or melancholia. Psychoses were treated. Epidemic encephalitis, cerebral vascular accidents, and alcoholics were also treated.

Therapy was not too successful because the hospital was only one block distant from the depot, and hospital trains arrived twice a week to remove the ill from Germany to the United States. The patients realized this, and I became convinced that the best therapy was discharge from the hospital with destination the United States.

When I received orders to return to the United States via Brest it

was necessary, in order to secure passage on a vessel, to assume charge of a group of neuropsychiatric cases, and take them to Army Hospital No. 1 in New York City. The types of cases were quite different from those examined and treated during actual combat. The group was made up of homosexuals and syphilophobias.

During the present World War II, as a member of a Medical Advisory Board I have disqualified for military service 80 per cent of the registrants examined. This high percentage of disqualifications is possibly the result of the experience gained in World War I.

In conclusion, I believe that the same neuropsychiatric problems will be met with in this war as were encountered in World War I, and that when ultimately the Allied Countries win the war, no small credit will be due the neuropsychiatrists who sincerely and conscientiously have performed the many duties assigned to them.

PREFRONTAL LOBOTOMY*

The Surgical Relief of Mental Pain

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AND

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PREFRONTAL LOBOTOMY¹ is the latest development in the field of psychosurgery, and thus far the most exact and controllable. It is the logical sequel to the local cortical extirpations carried out by Burckhardt² in the last century, to the transcortical incisions attempted by Puusepp³ before the first World War, to the brilliantly conceived prefrontal leucotomies of Egas Moniz⁴ and to the drastic prefrontal lobectomies⁵ carried out now and again by European and American neurosurgeons. By psychosurgery we wish to designate surgical operations upon the anatomically intact brain, in the effort to relieve mental symptoms. Psychosurgery is thus a far different procedure from the extirpation of tumors, cicatrices and other lesions that are causing symptoms and whose removal is imperative for reasons of survival or health. Psychosurgical operations are comparable to operations upon the sympathetic nervous system or upon the pain pathways of the central nervous system, in that anatomically normal structures are sacrificed in the interest of the health of the patient. Psychosurgery relieves mental pain.

It may be well at the start to admit that considerable prejudice exists in relation to psychosurgery. For many it would seem unjustifiable (to use no stronger term) to sacrifice man's greatest heritage, the frontal lobes, merely in the interest of his greater comfort and freedom from fear and self consciousness. Moreover, a gloomy picture exists of the condition of the individual who has suffered any considerable loss of frontal lobe tissue. We were all brought up on the story of Phineas Gage, the railroad construction foreman of a century ago, whose crow-

* Read October 22, 1942 in the fifteenth Graduate Fortnight of The New York Academy of Medicine.

bar was blasted through the top of his head.⁶ Some of us have seen the skull and the crowbar. Furthermore, we have followed with interest the studies on the functions of the frontal lobes from the time when Bianchi⁷ and Ferrier⁸ first called to our attention the changed personalities of the animals operated upon. The "tumor" studies followed, and then the "war injury" studies, and within the past decade there have been many cases of unilateral frontal lobectomy⁹ and a few of bilateral frontal lobectomy¹⁰ for tumor or for epileptogenic scars, with critical studies on the remnants of the patients' personalities. Out of these studies has come the picture of the "defrontalized dement," a being without shame and without ambition, lacking in all the finer qualities that make a man what he is, and debased to the level of the brute.

We do not wish to go to the other extreme and claim for patients who have undergone prefrontal lobotomy more than the average quota of virtues. Patients do lose something in the process, and we shall devote considerable time to the presentation of these defects. What we wish to emphasize is that in assessing the results of prefrontal lobotomy, the total behavior of the patient both before and after operation is critically studied, with whatever information can be obtained from the family and close associates of the patient. Just because the patient is relieved of mental distress and is again cheerful is no reason for calling the operation a success, even though a contented drone is more bearable than a complaining one. Enough patients now, have been returned to their homes able to manage them and to work for gain, who previously have necessarily been confined in institutions to make us optimistic about eventual results. It would seem that in certain cases the elimination of part of the activity of the frontal lobes has been of advantage to the total personality.

The problems in prefrontal lobotomy have gone beyond their first stage of hit-or-miss production of destructive lesions of the frontal lobes and waiting to see what the effect would be. With continued study of the procedure over the past six years, we have developed an operative technique that has certain merits of precision, and we have followed all of our 136 patients with periodic surveys, so that we know for these:

1. Where the induced lesions are.
2. What the results are to date.

It is well to conclude this introduction with a brief description of the operative technic.¹¹

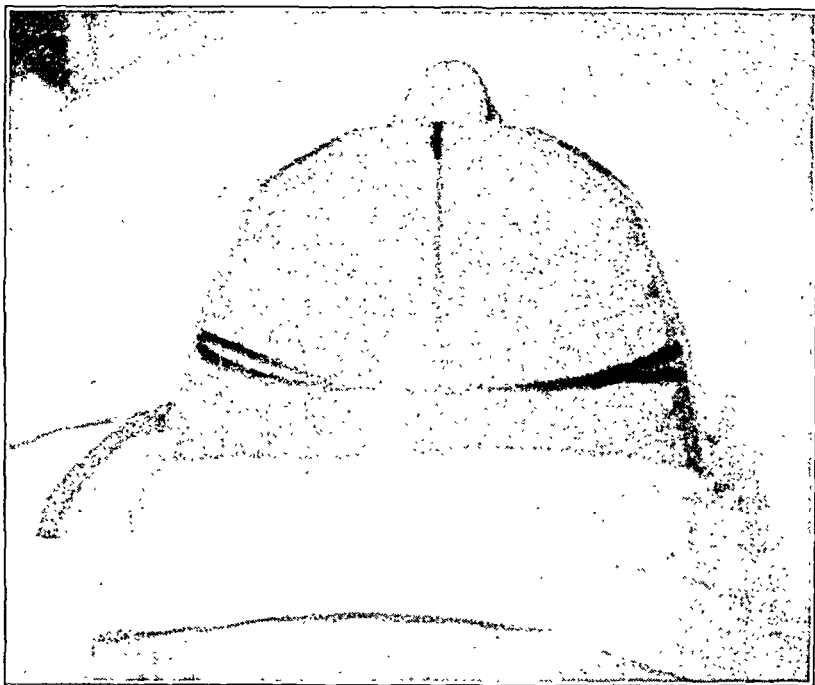


Fig. 1—Markings on the shaved and sterilized scalp indicate the midline and the coronal suture.

PREFRONTAL LOBOTOMY

We prefer local anesthesia, since the patient can then report his feelings and ideas as well as respond to tests. Only in disturbed or apprehensive patients is a general anesthetic necessary. The patient's scalp is shaved to the vertex and the coronal suture and midline are marked out on the sterilized scalp. The coronal suture is then exposed on each side by incisions 4 cm. long, going down through skin and muscle, and burr holes are placed in this suture 6 cm. above the zygoma. This opening is enlarged by small rongeur bites in the suture, the dura is opened and an avascular portion of the exposed cortex is penetrated by a sharp knife. The field is then prepared for coöperation of the surgeon and neurologist in making the subcortical incisions (Fig. 1).

The neurologist (or in his absence, the surgeon's assistant) sits behind the surgeon with his eyes in the extended plane of the coronal suture. Since this landmark is so constant and so easily outlined, it is closely adhered to throughout every operation, although deviations may be indicated under special conditions. The surgeon first finds the



Fig 2—A blunt knife, with hemostat attached, severs the subcortical white matter in the plane of the coronal suture.

midline by introducing a cannula directly toward the opposite opening. Resistance is usually perceived at a depth of 5 or 6 cm. If no change in resistance is felt, it means that the cannula has penetrated the knee of the corpus callosum; in which case the cannula is withdrawn and angulated toward the vertex until it impinges upon the falx cerebri, but always in the plane of the coronal suture. If the cannula enters the ventricle it is withdrawn and angulated slightly forward, but it does not seem to matter much if the incision does enter the ventricle.

A further landmark is found in the sphenoidal ridge by introducing the cannula downward toward the base of the skull. If the cannula penetrates more than 5 cm. it is probably behind the sphenoidal ridge and in the middle fossa, a dangerous area from the standpoint of bleeding. In such cases, reëxamination of the markings is advisable, since it is imperative to keep the incisions as close as possible to the plane of the coronal suture.

When the surgeon is satisfied with his landmarks, he clamps a hemostat on the shaft of a blunt knife (we use Killian's nasal septum periosteal elevator) and introduces the instrument to a depth short of the midline (beware the anterior cerebral artery!) and begins the fan-like incisions in the frontal lobe (Fig. 2). During this procedure the neurologist guides the surgeon, keeping the knife and the hemostat both in

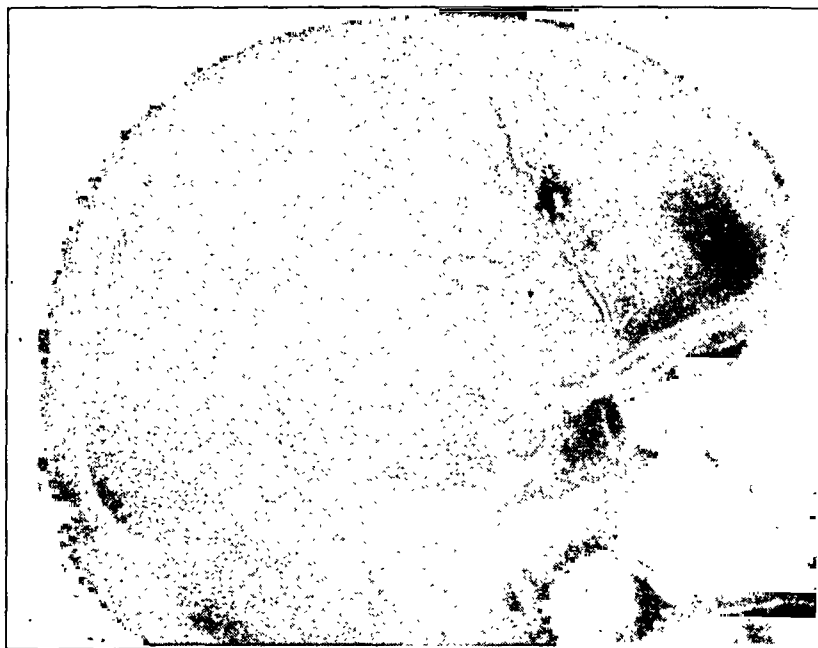


Fig. 3A

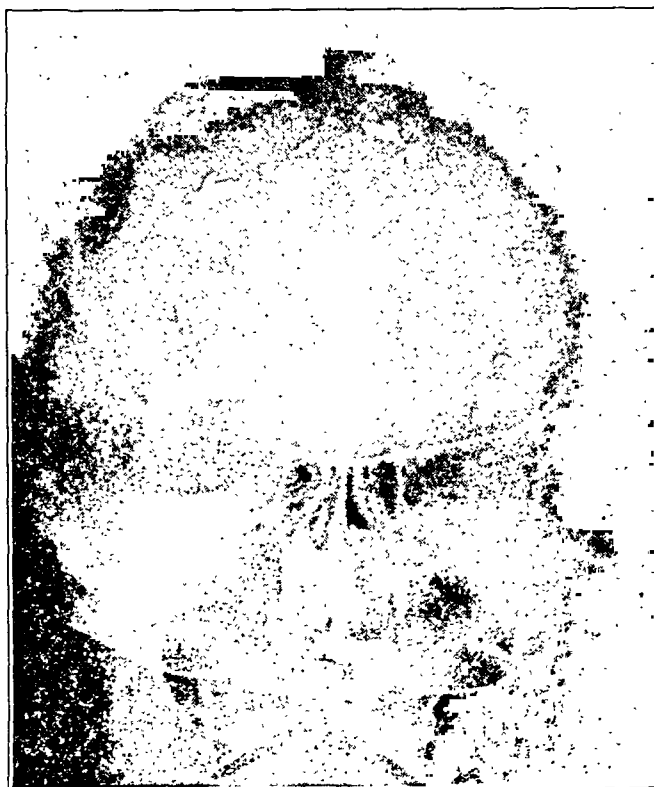


Fig. 3B

Fig. 3A & B.—Lateral (A) and frontal (B) roentgenograms showing the location of the lobotomy incisions.

the plane of the coronal suture, by means of constantly correcting the surgeon's tendency to deviate from this plane. The depth of the incision must be judged by the surgeon, any increased resistance being the signal for withdrawing the instrument as a precaution against lacerating an artery. Once the primary incision has been made, it is safe to deepen the incision by radial thrusts of the knife that will push any intruding artery before it and at the same time reach the more peripheral parts of the white matter in the frontal poles.

The upper and lower half of each frontal pole is thus transected subcortically, or in another manner of speaking, the 4 quadrants of the frontal lobes are sectioned. Bleeding is minimal unless the cortex is trespassed upon. At the end of the operation, iodized oil is introduced into the depths of the incisions for roentgenographic control (Fig. 3).

Secondary operations are not infrequently necessary. In some cases, if the roentgenograms show that the mesial portions have been missed, the incisions are reopened and the knife plunged deeper. In others, new burr holes are placed in the coronal suture or 1 to 2 cm. behind it and 3 cm. lateral to the midline, and fresh incisions made in the white matter of the superior frontal gyrus medially and laterally, to connect with the previous incisions, thus insuring more complete subcortical amputation of the frontal poles.

Shock is minimal and complications are few. The patient is able to stand and walk within an hour after operation, will even offer to get off the operating table and walk back to his room. Such offers are firmly declined! As soon as the stitches are out, he is encouraged to sit up and in a week or so to walk about the hospital. He can usually be discharged in ten days. We mention these facts in order to emphasize the mild effects of lobotomy as compared with lobectomy.

The mental state of the patient alters abruptly with the completion of the incision of the fourth quadrant, irrespective of which quadrant is sectioned last: upper, lower, right or left. Even with three quadrants incised, the conscious patient is still oriented, can carry out intellectual problems of considerable complexity, and, although quieter, may still report anxiety or distress almost as great as before operation. In a matter of seconds after incision of the fourth quadrant, the patient becomes unresponsive, disoriented, confused and is freed completely from his anxieties. Pulse and blood pressure fall rapidly to normal, the extremities become warm and pink, flushing and sweating occur over the ex-

posed forehead and the patient appears to go quietly to sleep. Some patients are more lively and engage the neurologist in lively and sometimes humorous conversation or even sing, on request, some wellknown song, say their prayers and so on. But they are unable to recall anything concerning their immediate surroundings, and even when the skin sutures are being placed, may deny that they have been operated upon. This disorientation is so characteristic that it is used as a yardstick for satisfactory operation. While it does not always occur on the operating table, if it is not present on the first postoperative day, it is likely that the operation will be a failure and that the preoperative symptoms will return within a short time.

POSTOPERATIVE CONDITION

The first few postoperative days are marked by phenomena that are quite peculiar to prefrontal lobotomy and are far different from the usual occurrences observed following most intracranial operations. There is no discomfort beyond slight headache, the fever may reach 102° F. for a day or two, the pulse and blood pressure are usually undisturbed, and aside from vomiting and urinary incontinence, there is little of note on the clinical chart. Patients are often reading, or rather, scanning newspapers or magazines on the second day, and they play with objects such as the bed light or the bell cord, or pick at their bandages by the hour. We have found that a rubber doll will absorb a lot of attention and divert it from the bandages. The appetite returns by the third day and the sphincters usually come under control within that same period. By the end of a week orientation returns, the patient still spends a good deal of time in relaxed idleness, and responds pleasantly when aroused. There is no aphasia and no ataxia, the only neurologic signs noted during this early period being a smoothing out of the facial expression, plateau type of speech and incontinence. A fleeting Babinski sign may be found, but seldom reflex grasping. Patients who have been sick less than a year usually admit freely that their worries and depression have lifted; those who have been sick for a long time will continue the same complaints if they are asked about them, but without the emotional intensity that marked the preoperative condition. Not infrequently, there are witty replies and a dash of profanity. Restlessness, talkativeness and singing are occasionally noted, but disturbed behavior is quite uncommon. With the beginning of the second week the



Fig. 4—Characteristic alterations in facial expression following prefrontal lobotomy. Schizophrenic of four years institutionalization. A. Before operation. B. Five days after operation. C. Six months after operation.

inertia clears, or the hyperactivity dies down and the patient is allowed to go home or to some institution for convalescent care (Fig. 4).

The convalescent period may last but three weeks or it may last for a year or more, depending upon the chronicity of the case, the operative success, the previous behavior of the patient and so on. It is during this period that the patient is learning to readjust to living conditions with an altered personality, and also bringing that altered personality into line with the accepted norms of his group. It is not always an easy task, either for the patient or for the family.

SOCIAL BEHAVIOR

The individual who has undergone prefrontal lobotomy is different from his prepsychotic self, although some indulgent families do not recognize the difference. He is apt to be more indolent, although some patients are very industrious; he is outspoken, saying the first thing that comes into his head rather than waiting an instant to judge the effect his response will have upon his audience. Patients acknowledge being hasty, undiplomatic, tactless. There is a certain directness of reply, maybe couched in the vernacular, that arrests the attention of the listener. When patients have said or done something that has undesirable con-

TABLE I

STATUS OF PATIENTS FOLLOWING PREFRONTAL LOBOTOMY

| <i>Disease</i> | <i>No.</i> | <i>Regularly Employed</i> | <i>Studying or Partially Employed</i> | <i>House- Keeping</i> | <i>At Home</i> | <i>Insti- tution</i> | <i>Dead</i> |
|-----------------------------|------------|-------------------------------|---|---------------------------|--------------------|--------------------------|-------------|
| Involuntional Depressions | 62 | 6 | 4 | 27 | 11 | 6 | 8 |
| Obsessive Tension States | 30 | 12 | 4 | 5 | 7 | | 2 |
| Schizophrenias | 31 | 4 | 7 | 4 | 11 | 4 | 1 |
| Psychoneurosis | 8 | 4 | | 2 | | 2 | |
| Undifferentiated (Schizoid) | 5 | 1 | 1 | 1 | 1 | 1 | |
| Totals | 136 | 27 | 16 | 39 | 30 | 13 | 11 |

sequences, they are genuinely sorry and often apologize. The emotional reactions are brisk, but shallow and short-lived. Patients laugh more, and flare up in petulance, but the storm is over almost before the family can prepare for it. There is none of the brooding melancholy, the hurt feelings, the grim silences. Consequently these patients can be treated a good deal like children, with affectionate references to their irresponsible conduct. They harbor no grudges.

The intelligence is intact. This is shown not only by formal tests, but also by the abilities as shown in everyday life and the working out of individual problems in occupation. The use of the intelligence is quite varied, however, depending not only upon its original quantity, but also on its training and more particularly upon the residual of self-consciousness and ambition that remains to the patient. Very complete subcortical amputation leaves the patient permanently crippled as far as effective use of the intelligence is concerned. Inadequate operation permits the return of the emotional distress that prior to operation prevented the patient from making effective use of his native endowment. A satisfactory operation relieves the misery and leaves the patient with his intelligence not only intact, but freed from the bonds of linkage with the self. We have taken particular pains to ascertain the occupational adjustment of our patients (Table I), and find that the majority are no longer dependent but are usefully even if not gainfully employed. When it is recalled that many patients in the younger schizophrenic

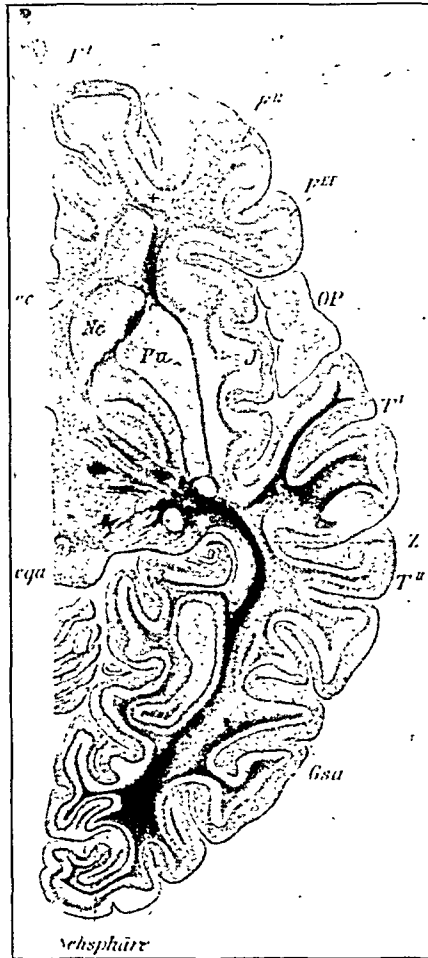


Fig. 5—Anterior thalamic radiation (+) in the 4 months child. This thalamo-frontal fasciculus becomes myelinated at a time when the association fibers are still immature [From Flechsig¹²].

group have never had jobs, and that the oldsters had retired, this record is not bad. Indeed, with two exceptions, patients who were working shortly prior to operation have been able to return to their employment.

The social behavior, then, is usually quite adequate, and the minor deviations are noted chiefly in hastiness and laziness neither of which is beyond the limits of normal, although both are novelties when the prepsychotic condition of the patient is considered. Teasing, exuberance, vulgarity, extravagance, gluttony and childishness are of uncommon occurrence after the convalescent period is past.

MODUS OPERANDI

As was mentioned in an earlier section, iodized oil is injected into the incisions at the end of operation for roentgenographic control. Furthermore, we have had the opportunity to examine a few specimens post-mortem from successful and unsuccessful cases. As nearly as we can judge, the successful incision cuts through the white matter of the frontal pole just in front of the anterior horn of the ventricle and the genu of the corpus callosum. It remains strictly in the frontal lobe, but may cut slightly into the sylvian fissure in its anterior extension. The white matter is not completely interrupted, there being bands of fibers of considerable size all around the fan-shaped incisions. Study of the architecture of the frontal lobe connections in relation to these incisions demonstrates that some fibers of the corpus callosum, some of the superior longitudinal and inferior longitudinal fasciculi and the occipito-frontal fasciculus have been interrupted.¹² The fasciculus uncinatus appears to escape. Most importantly, we believe, the anterior thalamic radiation is more or less completely cut across at this level, and the fasciculus cinguli is sectioned in some cases (Fig. 5).

We have been unable to detect retrograde alterations in the cells of the cortex of the frontal pole. On the other hand, the cells of the nucleus medialis dorsalis of the thalamus show important degenerative changes, which increase directly with the extent of the lesion in the frontal lobe. This is the nucleus that projects to the frontal lobe as shown not only by animal experiments, but also by myelinization studies, and even by gross dissection (defibrillation)¹³ of this part of the brain (Fig. 6). In summary, the operation of prefrontal lobotomy works through interruption of the system of fibers running from the thalamus to the frontal pole, without disturbing to any considerable degree the organization of the cerebral cortex. That some general shrinkage takes place in the frontal poles is evident in the gross specimens and also in the encephalograms taken on patients a couple of years after prefrontal lobotomy. The atrophy is slight in comparison with Pick's disease. The integrity of cortical activity is confirmed by the relative normality of most electroencephalograms taken some months after operation (Fig. 7).

A number of intelligent patients who have been able to furnish us with the results of their introspections have helped us to build up a certain series of ideas in regard to the effect of these incisions. Most im-

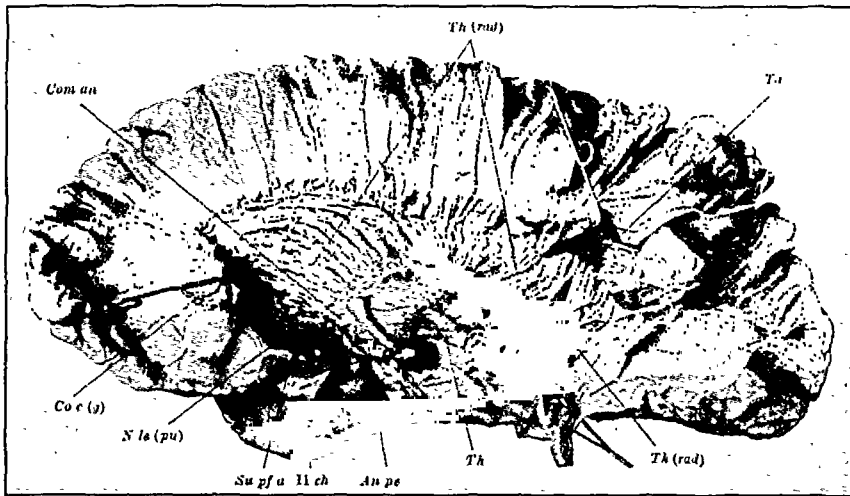


Fig. 6—Defibrillation preparation of adult brain showing anterior thalamic radiation [From Hultkrantz¹³].

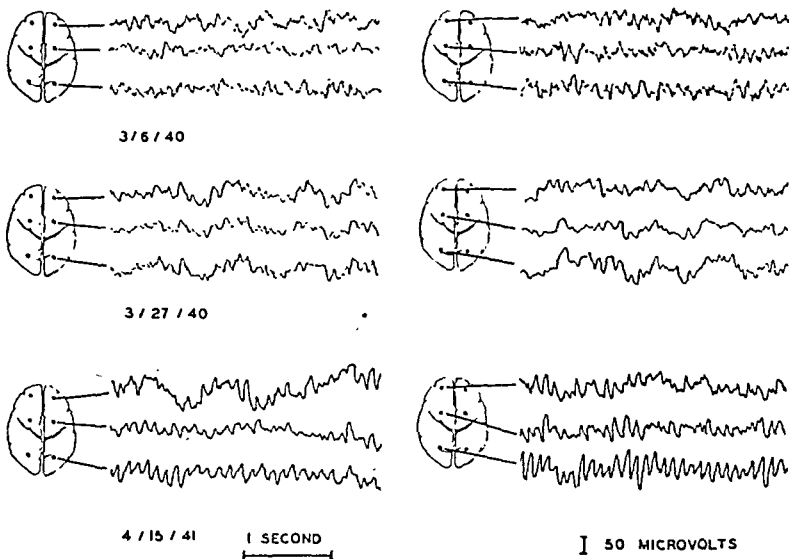


Fig. 7—Electroencephalograms from a case of chronic agitated depression [Kindness of Doctor Robert Cohn¹].

portant among these is that prefrontal lobotomy diminishes the interest that the patient takes in his own feelings, sensations, reactions and ambitions. At the same time, there is a vivid interest in things outside himself. All tests show this trend toward extraversion. The patient enjoys life because he no longer suffers from indigestion; he is tactless because he no longer considers the consequences of an inept phrase; he is indo-

lent because he no longer is driven to attain that ideal of the self that he originally set in life. It is a very personal reaction, and also, as far as we can judge, almost entirely an emotional one. Patients know that their clothes are too tight, but they continue eating; they know that their tasks weigh too lightly upon them, but they prefer to read the comics; they know that their profanity is offensive but they do not care to bridle their tongues. As one man said of his wife: "She's so full of don't-give-a-damnness." The operation of prefrontal lobotomy would seem to produce its effects by divorcing imagination and affect *as they relate to the self*. Imagination and affect are both lively but they are turned outward rather than linked to the individual himself.

In certain previous studies we¹⁴ have called attention to the function of foresight as being an important one carried out by the frontal lobes. We have observed this function badly disturbed for a period of time following operation, and then return. However, foresight in the recovered patient seems to turn much more to external things than to internal. This is shown in the successful occupational adjustment of patients whereas in their interpersonal activities, the qualities of abruptness, sauciness, tactlessness, and occasional lofty intransigence may furnish a startling contrast, particularly to the people who knew these patients previously as reserved, dignified, sensitive people. Patients know that they have behaved foolishly once the act is committed, and they may apologize for it but they cannot seem beforehand to form a mental picture of how they will appear after the act is performed, and even if they can, they do not have the emotional component that will restrain them altogether from saying the first thing that comes into their minds. We have often advised these people to get into the habit of counting ten before they speak, but they seldom get beyond five. It must be said, however, that their words and acts, once they have recovered their balance, seldom give offense. They are taken as ingenuous expressions of enthusiastic personalities.

PREFRONTAL LOBOTOMY AND PSYCHOPATHOLOGY

Prefrontal lobotomy reduces in greater or lesser degree the intensity with which the individual regards himself. Stated more succinctly, the operation bleaches the affect attached to the ego. Whether this is a good thing will have to be determined by examination of the relationship of these two functions in the sick individual rather than upon

theoretical grounds as related to the normally functioning personality.

The mentally sick individual is fundamentally a person whose ideational activities revolve largely around himself, whose interest in the outside world is more or less markedly restricted, and whose affective experiences largely dominate his behavior. The hypochondriac shows this just as clearly in the somatic field as the paranoid does in the social field. The obsessive thinker may have insight into the falsity or foolishness of his ideas but he is just as unable to control them as the schizophrenic is unable to control his hallucinations. Indeed, we have arrived at the opinion that it is not the ideas that matter; anybody may have the most abnormal ideas and still retain his mental health. It is the *fixation* that counts. When an idea becomes fixed, it is no longer harmless and may produce serious results. We have drawn the comparison of such fixed ideas with the sensitized photographic film. When light falls on such a film through the lens of the camera, there is a certain physical alteration in the silver emulsion that cannot be detected until a reducing agent is applied. Once the developer acts, the image is brought out. If the developer is allowed to act for a long time, the silver is all reduced and the image fades back into obscurity. If, however, at the proper time, a fixative is applied, the image remains in spite of further light and further chemical reduction. It is the *fixation* that causes the image to persist.

Now, in the case of abnormal ideas, as was said before, anybody can have them and still remain normal, but if such ideas become fixed, they have not only permanence but also noxious potentialities. And, if we are correct, it is emotion that fixes the ideas. Further elaboration of pathologic ideas consequent upon the fixation involves such phenomena as delusions, obsessions, compulsions, states of tension, suicidal ideas, and, through possible exhaustion and independent "firing" of different cortical areas, to hallucinations, stereotypy, mannerisms, verbi-geration and all the welter of schizophrenic symptomatology.

We do not insist upon acceptance of this concept of elaboration of psychotic symptoms, but it is quite noteworthy that prefrontal lobotomy is followed by loss of interest (affect!) in the hallucinatory and delusional experiences as well as in the bodily sensations, obsessions and so on, even though these phenomena persist for a time. As one very intelligent patient expressed it, "The sensation has moved from the center of my attention to the periphery." The cutting of the thalamo-

frontal radiation has thus deprived the ideational activities of their power to distress the patient. He is no longer affectively observant of his inner experiences and can therefore turn his attention to happenings in the outer world. The same pathologic ideational activities persist for a longer or shorter period, and the motor manifestations are brought under control even more slowly, but the bleaching of the affect has acted to return the ideas to the misty obscurity of the unimportant.

One might say that through the operation of prefrontal lobotomy, the destructive imagination of the patient is reduced to the point where he can again live at ease with himself and that the constructive imagination is relatively intact as far as external things are concerned. The great reduction in the consciousness of the self, however, renders the social readjustment of the patient a difficult matter at times, precisely because of his lack of concern about himself. Since it was his concern over himself and his own situation that seemed in large measure responsible for the mental breakdown in the beginning, the operation represents a radical attack, literally as well as figuratively, upon his psychosis. Furthermore, the disparate effects upon the patient and upon the family are apt to be of some moment in certain patients. If the patient is relieved of his burden of psychosis to the extent that his ebullience becomes a matter of uneasiness and hardship to the family, the result, from the social standpoint, leaves something to be desired.

We have to estimate the prepsychotic behavior of the individual before going ahead with the operation. Patients who have shown aggressive, psychopathic, criminal and alcoholic traits are refused operation no matter how clamorous they are, on the ground that their behavior after operation might be too offensive for social tolerance. Unfortunately for their families (the patients are always pleased) some cases have slipped by us without sufficient preoperative estimation and have proved troublesome problems. Also, we believed on theoretical grounds that alcoholics, if they were relieved of their states of tension would become good citizens. A couple of bitter experiences have taught us that prefrontal lobotomy is no cure for alcoholism. However, only one patient has developed alcoholism following prefrontal lobotomy.

RESULTS OF PREFRONTAL LOBOTOMY

The tabulated results of prefrontal lobotomy (Tables I and II) may be viewed as too optimistic, particularly after the foregoing discussion

TABLE II
RESULTS OF PREFRONTAL LOBOTOMY

| <i>Disease</i> | <i>No.</i> | <i>Results</i> | | | <i>Deaths</i> | |
|-----------------------------|------------|----------------|-------------|-------------|------------------|-------------------|
| | | <i>Good</i> | <i>Fair</i> | <i>Poor</i> | <i>Operative</i> | <i>Subsequent</i> |
| Involutional Depressions | 62 | 48 | 10 | 3 | 1 | 7 |
| Obsessive Tension States | 30 | 22 | 4 | 2 | 2 | |
| Schizophrenias | 31 | 21 | 5 | 5 | | 1 |
| Psychoneurosis | 8 | 6 | 1 | 1 | | |
| Undifferentiated (Schizoid) | 5 | 1 | 3 | 1 | | |
| Totals | 136 | 98 | 23 | 12 | 3 | 8 |

of the erratic behavior of the patients as described in previous sections. On the other hand, the figures include a number of patients who were operated upon during the first year of our endeavors (with the inadequate Moniz technique) and recent results have shown improvement. Moreover, with the passage of time there is often further improvement in the social adaptation of the patients, even through the third and the fifth year. This is in striking contrast with the results reported from the shock therapies, where relapses are not uncommon.

The factor of choice of patients is obviously important. During the first years, the emphasis was upon the involutional psychotics, and few schizophrenics were chosen for operation. Then, as relapses occurred from insulin and metrazol shock therapy, prefrontal lobotomy was employed in some of these cases. The patients selected were those whose families could afford rather satisfactory aftercare, and the majority of patients had not been institutionalized over any long period. It is not to be expected that results similar to ours could be obtained in chronic institutional patients, although we have noted some strikingly successful instances in patients hospitalized for more than five years.

It will be seen from the figures that the most successful cases are classed as obsessive tension states, with or without compulsions. These patients are intelligent and have considerable native energy drive, and they have not become dissociated. However, they are apt to be slow in making a satisfactory social adaptation because of the tendency to



A



B

Fig. 8—Photographs of a patient with agitated depression of eight years duration. (A). Before operation. (B). One year after operation.

aggressive behavior. In this connection, I may quote a paragraph from a letter received from the father of a patient: "A sense of gratitude, approaching mild elation is very noticeable, that his old difficulties are now gone forever. He speaks of getting married sometime and having children. Better judgment is also manifesting itself. He is not quite the

same David he used to be and probably never will be. With the passing of the intense, subjective emotionalism, a little of the good might also be lost, but this is of little moment, for a self directing hopeful personality is emerging, and this means everything."

The patients suffering from involutional depression are very satisfactory as a rule, although quite a number of them remain at home without useful occupation. In these cases, the illness has often led to retirement from business or domestic responsibility some time previous to operation, and the patients remain in retirement. We are particularly interested in relieving these patients of the burden of an over-worked conscience, believing that even if they are unable to resume their former responsibilities, they deserve a modicum of comfort in their advancing years. It may be argued that these patients respond particularly well to shock therapy and that prefrontal lobotomy is unnecessarily radical. Shock therapy has been tried unsuccessfully or with relapse in most of these patients. The others have been of the type that in our opinion would not respond satisfactorily to shock therapy (Fig. 8).

As far as schizophrenics are concerned, the results leave much to be desired. This is true, however, of any treatment with which we are familiar. The surprising thing is that so many of them have been able to get along outside of an institution even if not usefully employed. The patients in the other groups are too few for any valid conclusions.

SUMMARY AND CONCLUSIONS

1. Prefrontal lobotomy interrupts the connection between the frontal lobe and the thalamus, thereby reducing the emotional reactions of the patient as regards himself. This loss of painful self-consciousness in the psychotic patient is followed by reintegration of the personality with the ideational activities directed outward.

2. Intelligence is unharmed, but the application of that intelligence to the interplay of social and personal influences concerning the individual himself is diminished and in some patients results in indolence and lack of tact.

3. Many patients are able to reach their prepsychotic level of occupational adjustment. Some do even better.

4. Failures are due to:

- a. Inadequate operation. This may be corrected by a secondary more complete lobotomy.

- b. Too extensive operation. It is better to cut too little than too much.
- c. Inadequate evaluation of the aggressive traits of the patient previous to the development of his psychosis.
- d. Emotional deterioration. When the psychotic patient has given up the fight, it is probably too late for psychosurgery.
5. Old people whose lives are a burden to themselves by reason of psychosis are particularly good subjects for prefrontal lobotomy because of the serenity of disposition that follows operation.
6. Best results are obtained in obsessive tension states. Good results are obtained in involutional depressions. Fair results are obtained in schizophrenias. Poor results are obtained in alcoholism.
7. Finally, prefrontal lobotomy is comparable in its effects with the neurosurgical operations directed toward the relief of pain; only in these cases it is mental pain that is relieved.

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BRAIN ABSCESS *

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It is the intention of the author to present this paper in ordinary everyday language, having in mind the multiple interests of this audience in contrast to a group more specifically interested in neurology and neurosurgery.

A brain abscess may be located in the cerebrum, cerebellum or brain stem. This paper concerns itself only with those in the cerebrum and cerebellum. An abscess may be termed acute or chronic, for the sake of discussion, although the surgical definition of a true abscess carries with it the meaning that the lesion is circumscribed and walled-off. In the beginning of the process, the condition is that of localized encephalitis regardless of the method of introduction of the infecting organisms. There is an inflammatory leukocytic infiltration with edema. The surrounding brain substance becomes softened, breaks down and necrosis ensues. The necrotic area liquifies and becomes a small "core" of pus and detritus contained in an ill-defined cavity without a real wall. About this suppurative focus, necrosis of the brain substance lining the irregular, non-encapsulated cavity, continues with formation of more pus. The cavity is lined with shaggy necrotic tabs of hemorrhagic brain tissue. Beyond the necrotic zone there is a layer of markedly edematous brain substance. The edema is marked and extends most rapidly in single metastatic lesions.

The suppurative process may extend, without being limited, into the meninges or ventricle, which may prove fatal. Should the protective reaction of the brain be sufficient, the suppurative process becomes limited, the edematous area is lessened, the accumulated pus is walled-off or "encapsulated" and a chronic brain abscess results—a most fortunate occurrence.

The wall of the abscess may have a thickness of from 1 mm. to $\frac{1}{4}$ "

* Presented October 15, 1942 in the fifteenth Graduate Fortnight of The New York Academy of Medicine.

or $\frac{1}{2}$ ", the usual thickness observed being about 2 to 4 mm., requiring from three to five weeks in its formation. The wall may be so firm that the lesion could be mistaken for a solid tumor. In fact, instances are reported in which the entire abscess was removed as a tumor, and its true identity was not detected until sectioned.

The type of organism producing the abscess, and the amount of resistance offered by the brain substances, influence the formation of an abscess wall. In cases where certain anaerobic organisms are present, there is little tendency to walling-off. The wall may be quite firm, thick and resistant, due to the presence of a larger amount of fibrous tissue. On the contrary, some of the well-defined abscess walls, even though 2 to 4 mm. thick, are soft, friable and easily perforated or torn. All are not alike in this respect.

The wall is thickest at the pole of the abscess near the involved bone, external pole in temporal and frontal abscesses, and anterior or internal pole in most instances of cerebellar abscesses. The inner wall, the so-called "pyogenic membrane" is fairly smooth. The color of its inner surface is usually yellow or pinkish yellow. The outer wall usually has the dark brownish red color of a decaying cherry, or it may be gray.

In an early abscess that is not encapsulated, and before definite, firm encapsulation has taken place, the contents are not homogeneous. They consist of a supernatant yellow, oily, murky liquid and a residual thicker fluid made up of pus and brain debris or detritus. In chronic abscesses with a firm wall, the pus is usually thick and yellow or greenish-yellow. It may have no odor, or the pus may be very fetid and foul-smelling.

The shape of most abscesses is ovoid, with the smaller pole directed toward the infected bony cavity from which the infection spreads to form the abscess. Other abscesses, especially single, metastatic abscesses, are more likely to be spherical. In instances where the abscess has spontaneously evacuated itself through the cribiform plate or through the external auditory canal, the abscess may be the shape of a fig, surrounded by pericapsular purulent necrotic brain substance.

Abscesses most amenable to surgical treatment range from the sizes of a large malaga grape to that of an orange. The usual size is about that of a golf ball or a tangerine. The amount of pus contained varies from one or two teaspoonfuls to over seven ounces, the most observed by the author in which recovery took place. The average capacity is from one to three ounces in cerebral, and about one ounce or less in cerebellar.

Any of the pyogenic organisms may produce a brain abscess, the most common being *Streptococcus haemolyticus*. Some are due to the pneumococcus, the staphylococcus, colon bacillus, etc., or the organisms may be mixed. Some abscesses contain sterile pus. Anaerobic organisms probably play an important role, especially in metastatic abscesses.

SOURCE OF INFECTION, AND LOCATION OF ABSCESS

1. Otitic infections: mastoiditis, otitis media, necrosis of the petrous pyramid, thrombosis of the lateral sinus, etc.
2. Infections of the accessory nasal sinuses.
3. Metastatic.
4. Various diseases of the skull: osteomyelitis, malignancy, actinomycosis, etc.

Abscesses resulting from otitic infections are usually located in the homolateral temporal or cerebellar lobe, or both, the temporal region being more commonly involved. Involvement of the contralateral hemisphere may take place, in which the infection spreads through the sinuses. This is not common. The temporal portion of the temporosphenoidal lobe is involved more often than the sphenoidal. In the case of cerebellar abscesses, the outer inferior portion of the lobe is more frequently the site of the lesion, but it may be central in position.

An abscess secondary to infections of the nasal accessory sinuses usually involves the frontal lobe. It occupies, as a rule, the anterior pole of the lobe extending backward, upward and outward, external to and above the anterior horn of the lateral ventricle. However, it may be situated in the lower internal portion of the lobe nearer the falx and base than to the cranial vault. The homolateral lobe is usually the one involved but the abscess may be in the opposite lobe, and the lesion is sometimes bilateral.

Metastatic abscesses are single in about 50 per cent of the cases and may be amenable to surgical treatment, while 50 per cent are multiple and usually hopeless. Single abscesses are most common in the left cerebral hemisphere—fronto-parietal, frontal, parietal, or occipital, in order of frequency. The cerebellum is seldom involved. Single abscesses are usually large, originate in the white matter and encroach closely upon the lateral ventricle.

An abscess resulting from osteomyelitis may be single or multiple,

and is usually situated near or adjacent to the suppurative process in the bone.

Traumatic abscess may be situated in any part of the brain, especially when it is associated with a foreign body. The cerebral hemisphere, being more exposed to penetrating compound fractures of the skull, is more often the site of a traumatic abscess.

Let us now consider the individual abscesses—namely, temporal, frontal, cerebellar, traumatic and metastatic—with regard to their origin, symptoms and diagnosis.

TEMPORAL LOBE ABSCESS

Abscesses occur more frequently in the temporal lobe than in any other part of the brain. It is secondary, as a rule, to otitic infections and its presence may be recognized either before or after a mastoidectomy has been performed. A common picture is that of a patient who has had a chronic, purulent discharge from the ear for a long time, or, mastoidectomy has been performed and the patient is not doing well afterwards. The wound does not heal completely or as well as it should. There is a continuation of foul-smelling purulent discharge from the ear, or the discharge may have ceased rather suddenly. Cholesteatoma, with necrosis of the dural plate and pathological exposure of the dura, may be found. The cortex of the mastoid may be hard and eburnated like ivory, while the bony areas near the dura may be soft and partly destroyed by the disease. The abscess may have existed for some time and a mastoidectomy may not have been performed.

The infection spreads from the diseased area in the middle ear along the following pathways:

- a. Necrosis and perforation of the roof of the tympanic cavity. An extradural abscess may be present. The dura and other meninges become adherent to the necrotic bone area and to the brain, and the infection spreads directly into the brain substance and an abscess forms. Most of these occur in patients between 20 and 40 years of age for the reason that the roof of the tympanic cavity is much thinner and more friable in adults than in children. The external portion of the wall of these abscesses is situated very near the surface, may have a "stalk" connecting it with the diseased area in the skull, and may even perforate the wall spontaneously and discharge large quantities of pus through the external auditory canal.

b. Infection may extend or spread along the perivascular spaces of perforating blood vessels. In such instances the abscess wall is at a greater distance (1-3 cm.) from the meninges covering the temporal cortex. There may be no gross changes in the cortex.

c. Purulent thrombosis of the lateral sinus may be followed by abscess formation in the temporal lobe, but it is more frequently the cause of a cerebellar than a temporal abscess.

d. The infection may pass through the internal auditory meatus but this seldom occurs. Petrositis involving the tip of the petrus is more likely to produce meningitis than brain abscess.

Symptoms and signs of temporal lobe abscess: Symptomatology and neurologic signs vary considerably with regard to the stage of the development of the abscess. Pain in the ear, later in the head, is one of the first symptoms. The pain is located in the temporal region but radiates to the frontal and less frequently to the occipital region. It is not called a "headache" by the patient, but "pain." The pain is severe and sometimes excruciating, so that the patient may cry and moan. In children the crying is hard and prolonged and not the sudden short outburst of crying observed in well developed meningitis. The pain may be intermittent or continuous. Seldom does one fail to obtain the history of pain if the patient or family is carefully questioned. The pain is due to the rapid increase of intracranial bulk resulting from the suppurative encephalitis accompanied by marked edema. Loss of appetite and vomiting, not usually associated with nausea, occur early. A mild or severe chill, or chilly sensation is experienced early in most cases lasting from a minute or two to a half hour.

The pulse and temperature are elevated at first, more in children than in adults. There is no choking of the discs or engorgement of the veins at this time. There is marked prostration; the tongue is coated, and there is a foul odor to the breath. During this time, in the first two or three days, the diagnosis of the true condition is seldom made, though it may be suspected. High fever, stiff neck, and the Kernig sign are present only when meningitis accompanies the formation of the abscess.

Should the suppurative area not be limited, the process usually extends into the ventricle, meninges, or both, and suppurative leptomeningitis ensues, followed by death. Should the process be limited, and circumscribed and a definite wall be established, the symptoms and signs change in character and degree. The pain is not so severe in many in-

stances, but may be marked in others. The patient may not complain so much of the pain on account of the general diminished sensibility, diminution of the encephalitis and edema, or both. It is believed to be due for the most part to the former, i.e. diminished sensibility, for there is still marked increase of intracranial pressure, and the hemisphere containing the abscess is always much larger than normal. The patient as a rule becomes lethargic, stares vacantly, and there is a loss of cerebration and attentiveness amounting to a dreamy state. One may gain the patient's attention by sharply spoken words or commands, but soon he lapses into an inattentive, listless condition. The temperature ranges from normal to 102° F. Although some observers state that the temperature is normal, or even subnormal, most of the patients whom I have observed have registered a rectal temperature of between 100 and 102° F. No one has satisfactorily explained why the low temperature exists. The pulse becomes slow, and may be as low as 45 or 50 per minute or less. It may be normal, but not increased, except in complicated cases. The respiration rate is also lowered, but is usually regular.

There is rapid loss of weight. (On recovery, the gain is likewise rapid.) The breath is very foul and the teeth are covered with dirty yellow material.

Paresis of the face on the contralateral side is to be expected, but it never reaches the degree of paralysis seen on the homolateral side due to the physiological or anatomical interruption of the facial nerve by disease or operation upon the mastoid. Only in large abscesses, or in those with extensive edema does one observe paresis of the arm of the opposite side, and rarely is the lower extremity involved. Sudden hemiplegia of the opposite side is never seen except in instances of suppurative leptomeningitis or metastatic lesions.

Aphasia in some form is usually present in lesions of the left temporal lobe in right-handed patients, and vice versa. The most frequent form is anomia—the use of the wrong word. The next most frequent type is circumlocution—the inability to name an object though able to state its use. Motor aphasia is seldom observed and when it is one may know that the abscess is large and extends farther forward than usual.

Ophthalmological examination usually gives interesting data. The pupil may be dilated as a result of pressure on the third nerve. Seldom is the nerve completely paralyzed, and then only if meningitis is present. There may be paralysis of the sixth nerve with inability to look out-

ward, the nerve involvement being due to highly increased intracranial pressure or to concomitant petrous tip involvement. The most constant finding is engorgement of the retinal veins, usually more marked on the homolateral side. Hemorrhages, fresh and old, may be seen, especially in abscesses which have existed for several weeks. Papilledema is not observed early but may be marked, 3-5 diopters, by the time the patient comes to operation. The amount of swelling of the discs does not determine the size of the abscess. If the patient is coöperative, quadrant or hemanoptic defects may be determined. These are of value in localizing the lesion. Astereognosis is often demonstrated in coöperative patients.

The deep reflexes are usually increased, greater on the opposite side. The Babinski sign on the contralateral side may or may not be present. The abdominal reflexes are usually diminished on the opposite side.

Lumbar puncture often reveals clear fluid under pressure, well over 200 mm. of water. The cell count may be normal but is usually increased, 20, 50 or 100 or more per cm. Before encapsulation takes place the cells are predominantly polymorphonuclear cells. When the cells are predominantly lymphocytes, it is an indication that walling off of the abscess has been completed. Although rapid removal of a large quantity of cerebrospinal fluid may result in a fatality, it is not believed that the slow removal of about 2 cc. of fluid through a small needle for diagnosis is ever followed by untoward results. In fact, a careful lumbar puncture may at times be of therapeutic value.

The leukocytic and polymorphonuclear cell counts are increased as a rule, the former ranging between 11,000 and 18,000 with an average of about 14,000 cells per cm. and the latter from 85 to 92 per cent. Only in old chronic well walled-off abscesses is the count not increased. Radiographic films may be of some value, especially if a pathological exposure of dura has occurred.

You have heard the words "usual" and "likely" repeated. From this one can readily infer that all cases do not always present these signs and symptoms, especially when first seen by the neurologic surgeon. The patient may be in such profound stupor or coma that no history is obtainable from him, and very little definite information can be had from relatives or friends. On the other hand, the abscess may be so walled-off, benign and innocuous that no sign or symptom is present, and the fact that an abscess exists may not be determined except as an

incidental finding at autopsy. Such may be the extremes in signs and symptoms.

The abscess may become calcified and give no further trouble. The contents may become sterile, the lesion quiescent, and no trouble develop until the patient sustains a trauma, like a blow on the head. Then the abscess may increase in size and rupture spontaneously into the meninges or ventricle with fatal termination. One of these complications usually arises if the abscess is not successfully operated upon, but the patient may survive, ignorant of the presence of a brain lesion of any kind and die of other causes. The abscess may rupture spontaneously through the ear, but cure is not likely to be effected by so doing. Although death may result from greatly increased intracranial pressure which paralyzes the medullary centers, it is more likely to follow sudden rupture into the meninges or ventricle. In the former, death results in about 6 or 8 days, and in the latter, within 36 hours.

Diagnosis: One would be justified in concluding that a diagnosis should be made readily and easily after considering the points enumerated. In some instances this is so, and the diagnosis can be made almost as readily as in the ordinary cases of acute gangrenous appendicitis. This is not always the fact. At times diagnosis and localization of a brain abscess may be extremely difficult—sometimes even impossible.

Plain stereoscopic roentgenographic films should always be made. Air or gas may be present in the abscess cavity so that definite information may be obtained regarding the localization and size of the abscess. Shifting of the pineal body can be seen in certain cases.

Electroencephalograms are very valuable in the localization of cerebral abscesses. They are corroborative, with correct localization in about 72 per cent of cases. They are of doubtful value in cerebellar abscess.

When in doubt, one should resort to ventriculograms. Any case of temporal abscess which lends itself to operative interference will produce displacement and distortion of the lateral ventricles. Ventriculography is preferred to encephalography and is believed to be safer in these cases. Accurate localization of the abscess is most important if a successful outcome is to be expected. Indiscriminate exploratory punctures with a cannula, or exploratory punctures through an infected field can be mentioned only to be strongly condemned.

Temporal abscess should be differentiated from middle ear disease with adjacent edema of the brain, "serous meningitis," extradural ab-

sscess, sinus thrombosis, brain tumor, spontaneous subcortical hematoma, chronic subdural hematoma, and abscesses in other portions of the brain.

FRONTAL LOBE ABSCESS

An abscess in the frontal lobe gives rise to the same general symptoms and signs as a well developed abscess in any other part of the cerebrum, namely pain in the head, nausea and vomiting, foul breath, prostration, rapid loss of weight, slight elevation of temperature, slow pulse, fundi changes, leukocytosis, findings in the cerebrospinal fluid, changes in reflexes, slow cerebration, drowsiness, stupor and coma.

Localization and lateralization are usually much more difficult than in any other abscess. In fact, the neurologic findings may be very meager, almost to the point of being non-existent. When the general symptoms and signs of a brain abscess are present in a given case, the mere lack of localizing signs would make one choose the frontal lobe as the probable site. This is true especially if the abscess is small or has reached a very chronic stage. The abscess may be very large, almost unbelievably so, and it is only when the abscess or the surrounding edema is extensive that lateralization may be determined. As the abscess or surrounding edema progresses backward, the two most helpful findings present are aphasia, when the "dominant" lobe is involved, and paresis which the lesion produces. Paresis of the opposite upper extremity (weakened grip, etc.) occurs first, followed by that of the lower extremity, and last, if at all, of the face. In temporal abscess, the paresis is noticed first in the face, then arm, and last, if at all, in the lower extremity. Flaccid hemiplegia has never been observed except when the abscess has ruptured into the meninges. Rupture into the ventricle will otherwise occur before the abscess produces complete hemiplegia.

Dilatation of the homolateral pupil and unilateral loss of smell are of value in determining which lobe is involved. X-ray films of the sinuses and the operative site may suggest the side involved, although the abscess may develop in the frontal pole opposite to the operative site, or it may be bilateral. Frequently there is tenderness on percussion.

In an instance where one has very definite reasons for believing that an abscess is situated in a frontal lobe, exploratory puncture is advisable. If negative, ventricular puncture for ventriculography can be made through the burr hole. Where signs and symptoms are not of lateralizing value, ventriculography is preferred. The ventriculograms will show

marked compression and displacement of the ventricle backward and downward.

CEREBELLAR ABSCESS

Cerebellar abscess is more frequently found in children and younger people than in adults. The abscess is usually located in the lobe adjacent to the involved mastoid or lateral sinus or both, is more frequently situated in the external portion of the lobe, and is smaller than the usual cerebral abscess. Frequently it is the shape of a bird's egg, with the smaller pole directed forward and firmly fixed to the posterior surface of the petrus, from whence the infection extends. However, it may be centrally located within the cerebellar lobe.

From the foregoing one can readily understand what the signs and symptoms might be. As the abscess increases the size and shape of the lobe which it occupies, pressure is made across the midline, resulting in displacement of the medulla and brain stem, producing, as a rule, homolateral pyramidal tract signs, compression, and blocking of the aqueduct, causing internal hydrocephalus. This results in marked increase of intracranial pressure, bilateral papilledema, which may be equal, and bilateral frontal headache. Tenderness and pain on percussion may be elicited over that portion of the occipital region beneath which the abscess lies. There is frequently associated soreness and slight stiffness of the neck, more on the involved side than on the opposite. Nystagmus toward the affected side is usually observed.

Diagnostic lumbar puncture must be done with great care. Therapeutic lumbar punctures are banned. For relief of pain, ventricular puncture through a burr hole over the homolateral anterior horn is easily accomplished and should be done in every case. In most cases of cerebellar abscess observed by the author the patients were stuporous or in coma. Following ventricular puncture the mental condition clears up almost immediately and the severe pains are relieved. During this procedure air can be readily substituted for the cerebrospinal fluid and ventriculograms should be made. These will show the degree of the dilatation of the ventricles. On the antero-posterior film the lateral ventricles will show moderate symmetrical dilatation, and the third ventricle will appear dilated and in the mid line. On the postero-anterior view the posterior horn on the involved side will be smaller than that of the opposite side. This is due to the pressure exerted from below up-

ward by the increased size of the involved cerebellar lobe, the pressure being transmitted despite the intervening tentorium. In labyrinthitis this does not hold true; therefore, ventriculograms are valuable in differentiating between these two conditions. Aqueduct obstruction will also be demonstrated.

TRAUMATIC BRAIN ABSCESS

Traumatic brain abscess may follow various kinds of trauma such as punctured wounds of the skull and brain, compound fractures of the skull and gunshot wounds. The abscess may develop rapidly and show definite evidence of its presence in two or three weeks. It may form many weeks, months or years after the original injury. In a small punctured wound of the skull, dura and brain, the infection is carried directly into the brain, and the production of an abscess is due to direct implantation. This process may likewise follow extensive compound fractures of the cranial vault, but if the original wound is properly treated, and sulfanilamide is used, the subsequent formation of a brain abscess should be rare. Compound fractures of the base of the skull are much more likely to produce meningitis than abscess.

In some cases the original wound may have been sutured and well healed externally, only to be followed several weeks later by signs and symptoms indicating development of an abscess. Simple depressed fractures sometimes involve the mastoid and the frontal sinus and ethmoids in the fracture lines, allow release or spread of pre-existing infection from these structures into the fracture lines, and thus open pathways to the brain followed by abscess formation.

Associated with partial avulsion of the scalp, infectious material may be ground into the outer table of the skull, local necrosis of the skull may occur, giving rise to an abscess of the brain comparable to one complicating osteomyelitis of the skull.

An abscess may develop spontaneously from latent infection about a retained foreign body in the brain many years after its introduction, or shortly after removal of a foreign body which was retained for many years. In a case observed, a large abscess developed at the site from which a piece of knife blade was removed. The piece of knife blade measuring $3\frac{1}{2}$ inches in length with a saw-tooth edge, had been in the brain for over 28 years, the longest noted interval in the experience of the author.

Abscesses may appear early or late in bullet tracks, with or without retention of foreign bodies. When the abscess is secondary to a punctured wound of the brain, compound comminuted fracture with or without dural laceration, simple depressed fractures of the skull involving the mastoid or nasal accessory sinuses, its location is usually beneath and near the site of injury. Pus may be seen discharging through the wound, or there may be no discharge of pus. There is always a considerable amount of fibrous tissue formation in the structures overlying the abscess and the communication may be well walled-off. For these reasons, this type of traumatic abscess is especially amenable to operative interference. Another important bearing on the probable prognosis is that the abscess is single in about 90 per cent of the cases. Abscesses about deeply retained foreign bodies offer many more difficulties. Traumatic abscesses which do not communicate with the wound, and therefore do not discharge pus, present general symptoms and signs observed in cases of any well formed abscess of the brain. Should pus be discharging from the wound, symptoms and signs will usually be of a lesser degree on account of the continuous decompressive effect.

METASTATIC BRAIN ABSCESS

About 50 per cent of these cases are multiple, and therefore in most instances are hopeless. In cases of a single abscess, the surrounding edema and softening of the brain is more extensive than that present in any other form of brain abscess. It is always in the white matter. For these reasons earlier rupture into the ventricle, and not into the meninges, occurs. A fatal result ensues within two or three weeks in the majority of cases. On the other hand, encapsulation may occur, but all of these abscesses are large and encroach closely upon the ventricle. The intervening wall may be so thin that it appears translucent after evacuation and inspection of the abscess cavity, and there is grave danger of ventricular rupture from the ventricle into the abscess cavity if the post-operative increase of intraventricular pressure is not controlled by lumbar punctures.

Since the abscesses are usually in the fronto-parietal, parietal, or occipito-parietal regions, localizing signs and symptoms such as hemiplegia, hemianesthesia, homonymous hemianopia and aphasia, are frequently present and localization is readily made. Operation is performed on the sixth or seventh day.

Prognosis is good in all cases of single uncomplicated, well walled-off abscesses. This opinion is not universal, and previous to the last two decades, recovery was not expected by physicians or laymen. When a patient recovered, luck was thought to have played a big part. Sir William Macewen of Glasgow in his outstanding book "Pyogenic Diseases of the Brain and Spinal Cord" published in October 1893, held a different view and even then stated in one of the concluding paragraphs: "One might almost conclude that in uncomplicated abscess of the brain, operated on at a fairly early period, recovery ought to be the rule."

Treatment: All of the extradural foci should be eradicated. Operations upon the mastoid and sinuses, without the use of mallet and gouge, should have been completed. Many "brain abscess pictures" will clear up, due to the fact that the condition was caused by edema, extradural abscess, etc. At present the treatment of the abscess is surgical. This statement does not imply that the operation has to be done immediately in all cases. With the exception of cases of single acute metastatic abscess, it is best that the operation be done after the third or fourth week, at which time complete walling-off and encapsulation of the abscess is expected. The increase in the cerebrospinal fluid cell count, changing of the nature of the majority of cells from neutrophils to lymphocytes, is indicative of better encapsulation. Should operative interference be advisable, supportive dehydrating measures should be adopted. Blood transfusions may be indicated. Intravenous administration of 100 cc. of 50 per cent solution of sucrose is probably the best dehydrating agent. Its dehydrating effect is more prolonged than that of glucose; its results are striking in some cases of abscesses. It has been observed that a change from deep coma to that of clear mentality has followed administration of sucrose or glucose and the reverse was true when the solution was withheld.

When the proper time for operation on a cerebral abscess has been determined, the open method is preferred to the closed method of tube drains or tapping. With the open operation, advocated by the author in 1923 and used by him since that time, the overlying bone, dura and cortex are removed, the bony opening measuring about 2 to 3 cm. in diameter. Most abscesses amenable to surgery are situated not more than 2 cm., and frequently much less, from the dura. This has been observed many times at operation and in museums. Through a dural opening of the size suggested, after removal of the presenting portion of

the abscesses wall, the cavity is readily evacuated and inspected. Secondary pockets or extensions may thus be detected and dealt with. These pockets could not conceivably be drained by tubes through a small drain, as is used in the closed method. Slow controlled elevation of the floor of the abscess to the level of the skull accomplishes extinction of the abscess cavity, prevention of secondary pockets, rupture into the ventricle, and meningitis. Sulfanilamide and sulfathiazole gauze is used in the cavity. The entire area is healed in from 35 to 60 days. A scalp plastic with excision of the scar is done after six months. Cranioplasty—closure of the cranial defect with a tibial graft—has been done when a frontal defect requires it for cosmetic and protective purposes.

I wish to call your attention to the following observations regarding the use of a drainage tube in cerebral abscesses. In six cases in which colleagues have used a tube to drain the abscess, I have observed that a considerable amount of pus had drained out through the tube and the patient would improve for 4 or 5 days. Then the surgeon would notice that the patient was "not doing so well." When I was called to see the patient and removed the dressing, the end of the tube could be seen sticking up above the wound, in some instances with slight herniation of the brain and not a bit of pus exuding through the tube. Nevertheless, the patient would be quite ill. I would then be asked to take over.

With the patient placed on the side and the drainage tube directed upward, but still in place, a lumbar puncture was performed and cerebrospinal fluid was allowed to escape. Each time, after removal of about 10 cc. of cerebrospinal fluid, pus began to ooze out through the wound, both through and alongside the tube. As more fluid was allowed to escape, more pus exuded from the wound. The amount of fluid allowed to escape ranged between 35 and 45 cc. By the time this amount of fluid had been removed, an enormous outpouring of pus took place. After the opening in the bone was enlarged with rongeurs, and that in the dura and the brain cortex by means of electrocoagulation, the tube was removed and exploration of the tract was carried out under direct vision. One could then observe that the abscess cavity was partially collapsed about the tube, leaving three pockets, placed at thirds (or about 120 degrees) in the circumference of the abscess cavity, so that a cross-section of the cavity would somewhat resemble a three-leaf clover. These pockets were caused by compression of the brain abscess cavity against the tube from three directions, infolding the wall of the cavity

in such a manner that three pockets of pus were isolated from the tube and from each other. The appearance of the bulging portions of the abscess wall against the tube was not unlike that of the tricuspid valves viewed from the cardiac side. The valve corresponded to the bulging portion of the cavity wall, and the space between the valves corresponded to the small collapsed space leading to each pocket. The pus could not escape through the tube but remained and increased in amount in each pocket. Therefore, one could understand why the patient's condition became worse four or five days after initial drainage of the abscess with a tube had temporarily improved the patient's condition.

After 35 or 45 cc. (varied in the six cases) had been removed, the lumbar puncture needle was removed. Sufficient amount of decompression of the ventricles had been accomplished, the abscess cavity again became wide open so that only one cavity was present, and the pockets disappeared. Cross section of the cavity then would have shown it circular instead of the shape of a clover leaf. After removal of all remaining pus, the cavity was completely inspected and found to be similar in all respect to a "normal" brain abscess cavity. The cavity was then treated in the manner described—iodoform gauze, dakinization, etc.—and all six patients made uneventful recoveries.

The above described phenomenon is offered for the benefit of those who use tube drains through a small opening in the skull. The condition found might have occurred in cases treated by surgeons in this manner and been the cause of death in a number of cases ascribed by them to bad operative technique.

Drainage tubes are used *only* in cerebellar abscesses where there is no ventricle to be considered; where, in the majority of cases, the anterior pole of the abscess is fixed to the infected petrus by adhesions which should not be separated and where prolonged drainage of this area is proper. Furthermore, no elevation or herniation of the floor of the abscess should be permitted on account of shifting or torsion of the brain stem and medulla. Preliminary ventricular puncture should always be done, pre- and postoperatively if necessary.

RESULTS

Seventy-nine cases of brain abscess of all types, including those of metastatic origin, have been observed since 1920, and a number of traumatic abscesses and brain fistulae were observed during the four and

one-half year service with the German and American armies in World War I. A number of these abscesses had been previously operated upon or tampered with before coming under the observation of the author.

Forty-two of these patients survived, and thirty-seven died. Of the recoveries, eight were frontal, fifteen were temporal, nine were cerebellar, six were traumatic and four were metastatic. Two cases recovered after gross rupture into the ventricle, with associated meningitis, coma, and loss of sphincter control. They are now well. Four of the patients who recovered have died subsequently; one frontal a few months later of an unknown cause, and the others several years later. One frontal died of nephritis, and one in a drunken stupor with negative autopsy findings with regard to the operation. One cerebellar died of recurrence of the abscess, or formation of another abscess near the same site on account of an incomplete operation on the mastoid. The remaining thirty-eight are well so far as the abscess is concerned, and are either in school or at their usual occupations with two exceptions. Both of these were traumatic abscesses which resulted from self-inflicted wounds with suicidal intent in demented patients, both of whom are in institutions. The four metastatic abscess cases have some residual weakness of the operative side, in all of whom complete flaccid hemiplegia had existed. These four are otherwise well. The first survivor was operated upon 22 years ago, and the last, a traumatic abscess, was operated upon ten months ago.

Of the thirty-seven deaths, eight were frontal, ten were temporal, four were cerebellar, and fifteen were metastatic (3 single and 12 multiple). None were traumatic. In three of the early cases in 1920 and 1921, tube drains were used before the open method was introduced. In one frontal lobe abscess, the tube became displaced and in an attempt by an assistant to replace it, the drainage tube was placed into the brain substance outside the drainage tract; in one frontal, the tube perforated the ventricle; and in one temporal, the tube was removed too early and a secondary pocket ruptured into the ventricle. Eleven were multiple, metastatic, in both hemispheres and were, therefore, hopeless; three were large, single, metastatic abscesses in which the dilated ventricle ruptured into the evacuated abscess cavity through the thin intervening wall before the introduction of lumbar puncture to reduce intraventricular pressure. Two were acute abscesses, 1 with blood stream infection of staphylococcus aureus, while 1 patient was moribund and was

tapped only to satisfy the family. Six cases were complicated by suppurative leptomeningitis at time of operation, 1 bilateral frontal.

Four were cerebellar; one patient died following mastoidectomy, not operated upon for abscess but aspirated after death; one was moribund when seen, due to jamming of the conus in the foramen after repeated lumbar punctures by one of kind intent but poor judgment, and autopsy revealed rupture of the abscess against the pons; one early case in which the wire cone drain was used, and one patient in whom the abscess was not drained. One patient with frontal lobe abscess recovered from the original abscess and died later from a secondary abscess formed from reinfection, or lighting-up of the infection in an improperly operated frontal sinus. Ventriculograms would have located this abscess.

Four patients were operated upon according to the method advised and should have recovered, but died as a result of mishaps or accidents: 1 temporal, in a six year old girl who died of pneumonia following dakinization and being placed by an open window in the winter time; 1 temporal, in a distant hospital, removed the dressing and tore the brain substance by clawing with her fingers; 1 temporal, well walled-off, in a comatose woman who at the time of operation had a temperature of 104° F. and insufflation pneumonia, due to pouring eggnog down her trachea by a kind young nurse (at autopsy, egg and milk were found in the lungs); and 1 temporal in an unmanageable coastguardsman, who got out of bed on the sixth postoperative day, and the abscess ruptured into the ventricle.

Forty-four patients were operated upon according to the methods described, and followed by the management of the case as is now done. Of this number, forty survived and four died. Of the four deaths, two were due to preventable pneumonia, one to removal of dressing in a distant hospital, and tearing of the brain, and one to rupture of the abscess into the ventricle in a patient who was not controlled, and who got out of bed on the sixth day. Several of the earliest cases should have recovered had we but known the proper technique and management. The remainder were hopeless from the time of the first examination, some were moribund, and two were dead when first seen.

In all of the cases which recovered, only one operation was required for the cure of the abscess with but one exception. This case was one of multiple metastatic abscesses of the left cerebral hemisphere, secondary to an infected bone graft incision of the spine, in which case

nine separate abscesses were drained by a former assistant, Dr. Frank Turney. No patient has had postoperative convulsions except four, and these had convulsions before the operation. As experience with these cases has increased and early observation of the brain abscess suspect has been made, the results have improved.

The incidence of brain abscess and osteomyelitis of the skull, like mastoiditis, has been markedly reduced since the introduction of the sulfa drugs. In view of the fact that the vast majority of the brain abscesses observed in the past were secondary to otitic and rhinogenic infections, infected scalp and skull wounds and, in metastatic abscesses, pleuro-pulmonary conditions, it is possible that our work in these conditions will become almost extinct. It is possible that the sulfa drugs may sterilize the purulent contents of the abscess cavity, dissipate the surrounding edema and render the brain abscess innocuous, so that it may remain in situ without doing harm, or be easily extirpated in toto, like a tumor.

ON A BRAIN LESION CONSTANTLY
FOUND IN HEAD INJURIES*

JOSÉ ARCE

Professor of Surgery, Emeritus
University of Buenos Aires, Argentina

WHEN Dr. Ashford kindly extended me the invitation—for which I wish to thank him—to participate in the Graduate Fortnight on the Disorders of the Nervous System, I was all but compelled to decline. I am far from my usual place of work and, lacking all of my clinical records here, it would not be easy for me to prepare an address worthy of the Academy, which is our host, and of the distinguished audience that has met here tonight. But I could not fail to take into account the honor which such an invitation implied, coupled with the fact that I have but recently been made a Fellow of the Academy, and so I felt it was my duty to accept. This, then, is the reason why instead of hearing the words of Dr. William Cone, who was originally to be the first speaker on tonight's program, you will have to listen to me.

I take this opportunity to thank all Fellows of the Academy, and all individuals who have been instrumental in having my name added to the roster of my eminent colleagues of this Society, for the honor thus conferred upon me.

In accord with the program of this Fortnight, I have selected for my brief lecture a subject that follows the line of the topics to be considered in the present series of lectures.

This occasion also affords me an opportunity to render homage, once more, to the memory of my disciple and friend, Dr. Manuel Balado, whom death has recently torn from our midst when nothing led us to suspect that we might lose him, so full of youth and at the height of productiveness.

Together with him, a few years ago, we made some studies on the lesions observed in the brain consequent to violent traumas causing immediate or early death of the victim.

It is in these cases that can be studied the initial lesions caused by

* Read October 13, 1942 in the fifteenth Graduate Fortnight of The New York Academy of Medicine.

trauma, before they are transformed, changed or obliterated by reason of their evolution, as does or may occur when the patient survives a few days or is cured.

However, by their very nature, these accidents fall within the purview of the police and the judiciary, and consequently, common though they be, they are but rarely available for study by workers who are exclusively interested in the scientific aspects of the case. Most often, such workers have no chance to study medico-legal autopsy material until some time has elapsed, long enough to allow the anatomical condition of the tissues affected by trauma, to be profoundly modified.

We were fortunate, by special arrangements with the authorities in charge of handling such cases, to receive autopsy material, fresh and in perfect condition, sometimes no more than one hour or two after the death of the victim. This valuable material was immediately fixed in formol, and studied with minute care.

The histological specimens showed hemorrhages varying in size from punctate to hematomas, the size of hazelnuts, and more or less confluent; but then they also revealed the presence of fluid separating the cells and nerve fibers, and saturating, as it were, the nerve substance. It was as if a large quantity of plasma had extravasated. This true acute cerebral edema, we believed, caused compression more severe than that produced by the extravasated blood, for the simple reason that it affected the entire brain, both close to and away from the hemorrhagic areas.

Study of numerous preparations from different parts of the brain and many different accident cases demonstrated to our satisfaction that this acute cerebral edema was the real cause of acute cranial hypertension, and of such intensity as to be able, alone, to cause death of the patient.

This observation explains certain findings which seem paradoxical at first sight: patients brought in with skull fractures and visible injuries, presenting a very serious picture, do survive, while others, with neither fracture nor visible injuries, die either directly in the accident or shortly afterwards.

However that may be, and I do not propose to examine the pathological aspects of these cases, one fact emerges conclusively established. It is the constant presence, from the first, of severe cerebral edema in head injuries, independent of the subsequent evolution of the lesion.

For the reasons here shown we are as a rule averse to operating on

patients with head injuries. That is, unless local lesions present special and urgent indications for an emergency operation, we prefer treatment by absolute rest and prompt removal of the hypertension.

And how is that to be accomplished, you may ask. This is the way: Every eight hours, 20, 25, and 30 cc. hypertonic saline solution, let us say, of 20 per cent concentration, are given intravenously. This hypertonic saline draws the extravasated fluid into the circulation, drains the entire brain, produces decompression, and in this manner effectively controls hypertension.

The treatment may be combined with the classical treatment directed to decongestion: purgatives or drastic enema, or both at the same time, depending on the case in hand.

For the first we are not interested in finding out whether fracture has occurred, because roentgenography requires moving of the patient. Nor do we seek to establish whether the cerebrospinal fluid contains blood; accordingly we forego lumbar puncture except in cases where the symptoms do not yield promptly to intravenous injection of hypertonic saline.

Our results from the systematic application of this method have been good. On this account we hold that treatment in similar cases should consist of absolute rest and cerebral draining by the technique I have outlined to you.

This, in sum, is the anatomical fact which I wanted to bring to your attention, especially because it furnishes the basis for an efficacious treatment available to every physician, when aid of a specialist cannot be secured.

At the outset of this brief address, I felt impelled to recall to you the memory of the man who was the first teacher of neurosurgery in Argentina, my pupil and dear friend, Dr. Balado. Permit me to add a few words. It was he who originated and taught the world the technique of ventriculography with iodized oil as radiopaque medium, which enables us to appreciate lesions which are difficult to discern by means of ventriculography, using air. And to him we also owe detailed studies of the optic paths in their relations to the geniculate bodies and the calcarine fissure, as also of the disorders caused by chronic meningitis localized about the chiasma. In recent years he devoted concentrated study to the electrical currents which can be registered in the cerebral cortex. His life was dedicated to study, observation and the progress

of neurosurgery.

If I have paid tribute to his memory in your presence, it was also with the purpose of showing to the young generation and those who disbelieve in the virtue of work dedicated to the furtherance of science, how much can be achieved, even in the regions of the human organism most difficult of access—if there is the will to contribute a something for the benefit of all mankind.

Sadly we must recognize that peace, justice and freedom are not always with us. Yet these are the three conditions essential to elevating the level of civilization, threatened as it is today by those who want to confound us by boasts that they are our betters because they have the brute strength to attain the objects of their ambitions. But for all that, we must continue to apply ourselves to our work, for ultimately science and civilization will prevail.

LIBRARY NOTES

THE JOANNA STEPHENS
MEDICINES FOR THE STONE**A Faith That Failed*

EDWARD L. KEYES

My under-
Scoring.
R.

"There are Many cured of Diseases by the Imagination only; for Nature often submits to the Thoughts and vehement Desires of the Soul and, our Spirits being affected, the Body is affected also."

(Words taken from a *Treatise on the Stone and Gravel*, by John Greenfield, published in 1710; in which year, let us assume, Joanna Stephens may have been born.)

It is an equal honor, gentlemen, you have done Medicine and myself, inviting us to appear before you. For myself, let me thank you truly but briefly, for I can not be sure that my gratitude is a major interest of yours. And I have scarcely the right to stand before you in the name of medicine since *Anno Domini*, the malady no one escapes, has stricken my name from the register of physicians.

It would, indeed, be more appropriate if I spoke this evening only of that mighty and merciful man to whom we owe my presence here. Throughout my life I have watched with awe the lustiness of Sam's laughter. Like his language it was free and gay beyond anyone else's on the south side of thirty-fifth street in the block where the Swedenborgian church stood, between Park and Lexington. I know, for I lived on the north side of thirty-fourth street and, on summer evenings, the yards between would echo with a hearty roar to which his brothers could retort only with lesser bellowings. . . . I have watched him grow more purple than the rest of us and then falter, as I begin to do, but all with a Johnsonian magnificence and gusto such as, perhaps, you will not see again in these rooms he loved so well.

He was happy here and I, who know how devoted a bibliophile he was, share with you the secret that laughter and ready expletive were part of his ebullient way of denying credit to himself. He was or, may I say, he is of that happy company who have learned how to curb to the service of humanity a seemingly boundless masculine vigor. The most characteristic yarn about him—pardon me the pleasure of repeating it—tells how a patient in the Presbyterian Hospital begged that Dr. Lambert might come to her room and, when he came, said, "Doctor, I had to see you. For days I have been listening to you swearing so beautifully at the woman in the next room that I just had to have you in to swear at me a little. I do so need to be cheered up."

With none of the self-consciousness of Tennyson's Sir Galahad, Sam's strength was as

* Read April 16, 1942, by invitation of the Grolier Club through the late Dr. Samuel W. Lambert, at the opening of its "Exhibition of Books on Healing by Faith, Fraud and Superstition in the Eighteenth and Nineteenth Centuries," arranged by Gertrude L. Annan, in charge of the Rare Book and Manuscript Rooms in the Library of the Academy. The list of books shown appears in the *Bulletin of the Medical Library Association* for October 1942.

the strength of ten because, for all the flotsam of youth that still found harbor in his talk, his heart was pure gold.

Restless spirit, may you roam eternity as gay and vivid as we knew you here.

But we must on with our business, gentlemen. The documents amid which you sit are medical in a sense, yes, but psychologically they are the history of resurgent error, of the hope deferred that maketh not the heart sick. They exhibit humanity in pursuit of the goddess, Panacea. Throughout history the relation of physician to patient has been a priestly one almost exclusively until, slowly and painfully and against the united opposition of the senior licentiates of each succeeding generation, man's skepticism as to his own infallibility forced itself to the fore and the human race began to grow up.

We still have growing pains. Today you will still find plenty of men ready to cast the first stone at the scientific method, failing to recognize it for what it is, our only measure of precise reasoning. We are far from being adult collectively, however ageing individually.

Meanwhile, struggling for room to live in a slightly imperfect world, we need Courage and Faith; Courage to carry on and Faith when Courage fails. Integrity we need as well, I grant, and Charity, the greatest of all, and some would say Hope, though you might dispute this; the martyrs to duty show an effective Faith, child of Habit and Hopelessness. One needs hope only to get set in one's habits; we drop our hopes one by one in the journey through life and camouflage our loss even to ourselves.

So here around you are the banners of faiths outworn, the texts printed on them rallying cries to forgotten panaceas. Laugh at them gaily as you will but, in the present state of our ignorance, do not forget how human they are. The heroes of medicine had their panaceas, too.

* * *

Tonight let me chat with you about a panacea, a lesser one, the distinction of which is that it swept the civilized world for a moment, won a grant from the British government, and initiated a series of cures for the stone that held a place in English pharmacy for a century or so.

When I was a medical student my father used to regale me with yarns of other days in medicine. One of them I never forgot. It concerned Joanna Stephens and the purchase by parliament of her secret remedy for the stone.

When I came to look up Joanna Stephens, for the purpose of writing this paper, I found her rather a dim figure but the persons who backed her were notables. Two of them, Hartley and Hales, still linger in the Britannica and have monuments in Westminster. They were wrong, these men of the XVIII Century, but since there was no cure for their stone save an operation more crude than infallible, their wrongheadedness must often have brought them greater happiness than right thinking could have done. 'Tis folly, sometimes, to be wise.

The year was 1737. The Old Style calendar was going out of use in England and the fashion of beginning your nouns with a capital letter about to disappear. George II was by the grace of God king and Robert Walpole, by the grace of Queen Caroline, prime minister. Across the channel Louis XV was beginning his long reign and beyond the ocean Benjamin Franklin, from whom we shall hear, was entering his thirties. John Wesley was "riding the roads of England."

To comprehend the situation you must know, as the contemporaneous world did not, that a stone in the bladder, as it grows larger, may excite less and less pain. If a fellow happens to have no great pain at the outset, his stone may later bother him so little that he forgets he ever had a pang. This is not always kept in mind by the doctors of today, as witness their surprise at the report of a number of such cases of "silent stone," as they are called, before the French Urological Society in 1918. The patients were seemingly healthy footsoldiers without a pain in the world who, after three years in the trenches, were delighted to learn that a cloudy urine might qualify them for a stay in hospital. A

number of these would-be malingerers were found to have huge bladder stones.

So: Joanna Stephens is introduced to us by David Hartley, A.M., F.R.S. Hartley is known to fame as the founder of the English school of Association Psychology. Such was the impression he made on his generation that forty years after his death Samuel Taylor Coleridge named his first-born son Hartley. His great work, "Observations on Man," though not published until 1747, was being written when he fell under the influence of Joanna. This was in 1737. Up to 1742 Hartley practiced medicine (though never an M.D.) in London, and thereafter in Bath. When he met Joanna he was 32 years old. A few of his prefatory remarks about her will give you a notion of his candor.

"It is now more than a Year that I have had the usual Symptoms of the Stone in the Bladder, with some Suspicion of that in the Kidneys. This made me listen to the Accounts of Mrs. Stephens's Medicines and, upon inquiring into some Cases, I was encouraged to try them. I have since been much more particular in my Inquiries and here offer ten Cases to the Publick, with an Abstract of some Experiments taken from a Journal which I kept of them. . . . As to myself, I am neither an Evidence against the Medicines nor for them, excepting that since the Use of them I have voided several angular Bits of Stone in so soft a State as to crumble easily. . . . My design in printing these Cases and Experiments is to engage the Publick to purchase the Discovery of these Medicines of Mrs. Stephens. She offers this at Five Thousand Pounds and is ready to submit the Effects of the Medicines which she discovers to any Examination which Gentlemen of Worth and Skill shall propose. It is easy to see how much concerned I am to know what these Medicines are which I take daily. But the Benefit which many Persons have plainly received from them in painful and dangerous Cases and my Opinion of their Efficacy in dissolving Stones of the Kidney and Bladder would render me inexcusable, if I did not use my best Endeavours to make them of general Service."

The first case cited is that of the Reverend, the Bishop of Bath and Wells. Let us spare his blushes.

Hartley tells us that Joanna "is the Daughter of a Gentleman of good Estate and Family in Berkshire. About twenty Years ago she accidentally met a Receipt for the Stone, consisting of Egg-shells dried in an Oven and powdered"—Lime salts for the treatment of stone are first mentioned by Pliny—"but finding it caused great Costiveness, she added a small Quantity of Soap"—and here spoke her genius—"to each Dose, with a view both to prevent this Inconvenience and to forward the Dissolution of the Stone. . . . About twelve Years ago she gave her Powder to one Mr. Coxon, adding thereto very frequently half an Ounce of Soap Decoction. He had Symptoms of the Stone in the Bladder, voided many Scales during the Use of the Medicines, and received a more remarkable Cure than any Person before him had done. Upon this she gave the Powder and Soap in still larger Doses and found them attended with proportionately greater Success."

"In the Year 1735 the Hon. Edward Carteret, Esq, Postmaster General, began taking Mrs. Stephens's Medicines and received great Benefit from them. This engaged the Attention of the Publick and more particularly such as were afflicted with the Gravel or the Stone, so the Number of People who took them increased every Day. In the Year 1737 the Cures performed by these Medicines were so many and so well attested that the speedy Publication of them was judged to be of great Importance to Mankind."

Two years after his first publication Hartley was again in print with "A View of the Present Evidence for and against Mrs. Stephens's Medicines as a Solvent for the Stone." This little essay, like its predecessor, seems a masterpiece of candor combined with complete subjection to the prevailing winds of doctrine. The experiments were soundly conceived to compare the solvent effects on bladder stones of (1) water, (2) water containing the medicines, (3) normal urine, and (4) Hartley's urine while he was taking the medicines. The last was far the most effective solvent, a result we should attribute to its alkalinity and bacterial content, factors one could not suspect in 1737. Moreover, the experiments were confirmed and expanded the following year by Morand in Paris and by

the Rev. Stephen Hales, F.R.S., who is remembered as the first experimenter on the phenomena of the blood pressure and who was a botanist of note. (Yet it is for his experiments on the Stone that he got his F.R.S.)

Were there a recording angel for science, these documents would be blotted with his tears, so earnest are they in effort, so searching in method (considering the then state of knowledge), so human in error. The supporting cases, though, are happy for most of them show great improvement during treatment—this treatment now so dead and always so disgusting! Drinking three pints of soapsuds a day, no wonder some of the victims revolted! Yet among the 152 patients whose cases are reported by Hartley, the 124 who seem to have had stone were, about two-fifths of them wholly relieved, two-fifths of them improved, and only one-fifth of them unrelieved or unable to stomach the medicines.

In those days they took it for granted that one got hard usage from one's physician. For example, twenty grains of calomel with as much jalap was the standard cathartic until Hahnemann earned the gratitude of mankind, not by his homeopathy but by his practice which spared man such unwholesome and unnecessary cruelties of physic. Even after Hahnemann, the impotence of physic was such that at Bellevue Hospital, in its early days, the wards were allotted a pint of whiskey a day per patient.

But I stray from my Joanna. Subscriptions were solicited toward the desired £5,000 and when these fell short, the list of subscribers was published, headed by the names of two bishops, an earl, the Rev. Stephen Hales, and Lady Betty Germaine, and ending with two physicians and the Duke of Kent. There were 187 names, down for £1,400.

But Joanna held out for her five thousand and since, following publication, subscription was not stimulated, parliament was petitioned in her name and, a year later, an act was passed providing "a Reward for Joanna Stephens, Spinster, upon proper Discovery made by her for the Use of the Publick of the Medicines made by her for the Cure of the Stone."

The committee of thirty appointed to pass upon the efficacy of the treatment included three archbishops, the Lord Chancellor, the Chairman of the House, six physicians and three surgeons, among them the leading stonecutters of the day, natural antagonists to the method.

The committee met the day it was appointed. Before them appeared four persons to testify that, having suffered the symptoms of the stone, their bladders had been searched by several qualified persons and the stone touched. Then they had taken the Stephens medicines for a number of months, had been relieved of their symptoms after passing (in all but one instance) fragments of stone and, thereafter, had been searched and no stone found. Twice the preliminary attestation as to the presence of stone and, for the lot of them, the final attestation that stone was no longer present, had been made by members of the committee. Stronger evidence of cure, personal and professional, could not be had.

You who complain of your hospital fees will be interested to know that the final examination of two of the witnesses was made at Child's coffeehouse in St. Paul's churchyard.

Thereupon the committee, having received from Joanna a description of the drugs and their manufacture and use, certified that "we have examined the said Medicines and are convinced by experiment of the Utility, Efficacy and dissolving Power thereof." Two meticulous members of the committee dissented as to the dissolving power, not as to the utility and efficacy.

So the £5,000 was paid to Joanna and her disclosures published in the *Gazette*. It thus appeared that, beyond a few charred herbs, there was no secret, only the soap and lime water. So, to support their faith and to prove their prowess, scientists gave battle as to the relative merits of the lime obtained from sea-shells and that from limestone and whether suds from Alicante soap were or were not preferable to those had from Castile. (Soap had been used in England but a century and the best still came from Spain.) Then followed the modifications, the "lixivia" of Hartley, of Hales, of Whytt, of Justin.

Within five years the treatment assumed quasi-official form in "An Essay on the

Virtues of Lime Water in the Cure of the Stone," by Robert Whytt, M.D., F.R.S., president of the Edinburgh Royal College of Medicine. He prescribed an ounce of soap and three pints of limewater a day. Of the soap he said pleasantly that not only is it "endued with a considerable Power of dissolving the Stone but likewise it will destroy all acid Humours of the Stomach and Guts and contribute greatly to keep the Belly easy and prevent Costiveness that might otherwise be occasioned by the Lime Water."

Meanwhile, in 1744, the prime minister, Robert Walpole, died miserably of an undiagnosed retention of urine. During his illness he had the misfortune to pass some gravel and so escaped from his surgeon, Ranby, long enough to permit Dr. Justin to make him a bit more miserable with lixivium and to draw from Ranby two priceless vituperative letters that recount the last illness and autopsy of the victim. Twelve years later Horace Walpole, brother to the minister (and not the epicure of Strawberry Hill) died peacefully with stone, though perhaps not of it, after having published in the second edition of Whytt an account of his "cure" by soap and limewater. They do say that when he was "opened," as the phrase was, the three stones found in his bladder were quite small.

Experiences of this sort plus publication of the mystery dissipated the novelty and threw doubt upon the infallibility of the cure but the faith of true believers remained unshaken. The last publication of David Hartley on the remedies seems to have appeared in 1746, the second edition of a Latin essay, reviewing the subject and citing, among others, six cases, puzzling to him, of persons whose symptoms had been relieved by the treatment, but who still had the stone. But Hartley was still enthusiastic over the grit that passed from his bladder in this, the ninth year of medication and expressed the hope that, with God's help, his symptoms, though not yet greatly diminished, would soon cease. They did after another ten years.

How helpful the creed was and how it withstood the factual shock is expressed by such contemporary authors as I have unearthed. When Edward Carteret died of apoplexy in 1743 he had twice been reported, as we would say, practically well, so the two stones they found in his bladder probably gave him little pain.

In Blackrie we read of a young shoemaker seven years a martyr to the stone who, between November 1756 and June 1757 ingurgitated 17 pounds weight of soap and 1500 pounds of limewater and "in three or four months after he began his Course found himself as easy as any Person who was never troubled with the Stone . . . and tho' when dismissed from the Hospital he forbore the Use of these Medicines and lived at large, eating plentifully of Salt and acrid Food which he was fond of, yet notwithstanding about three or four months afterwards . . . upon searching, the Stone was found in his bladder."

Perhaps as sagacious a comment as one encounters at this period is that of Benjamin Franklin who, in 1752, writes his brother, a stone man as Benjamin himself was later to be, "I have read Whytt on Lime Water. You desire my thoughts on what he says. But what can I say? He relates Facts and Experiments and these must be allowed good if not contradicted by other Facts and Experiments."

Joanna's fame must have persisted for much of her lifetime. The steps in its decline are a bit vague. The bigbugs doubtless took over and, like Whytt, emphasizing the lime-water and using the soap, dimmed her luster. Leroi d'Etiolles has a good word for Joanna in 1825 and Sir Henry Thompson, one of the fathers of the modern school, mentions her in 1888.

* * *

But I have held you too long by the stony roadside of my beloved profession. To you, no doubt, what interest the story has is the confusion of motives we sense in Joanna and her followers. Was she anything more than a charlatan dazzled by the wonders of the soaping she gave the world? We do not know. And Hartley, how much did he get of the Five Thousand Pounds? We do not know. And the Rev. Stephen Hales, how did that lucid mind come to assent to the prevailing hysteria? Again, we do not know. And why Whytt "On Lime Water"?

Our scientific education has progressed much in the two centuries since Joanna flourished. Yet speed in transit and physical rather than intellectual illumination are all that most men have to show for this. We are better informed than our ancestors but we have less time to digest our information. The mob of men, even the mob of men of letters, remain uneducated because matters of moment and matters of the moment are not identical: We look outward, seeking novelty. Man is imprisoned in the external present.

These last words are Gilbert Murray's. Let me quote the paragraph in the *Religio Grammatici* in which they appear.

"Man is imprisoned in the external present and what we call a man's religion is, to a great extent, the thing that offers him a secret and permanent escape from that prison; a breaking of the prison walls that leaves him standing, of course, still in the present but in a present so enlarged and enfranchised that it is become not a prison but a free world. . . . And a scholar, I think, secures his freedom by keeping hold always of the past and treasuring up the best out of the past, so that in a present that requires resignation or courage he can call back the spirit with which brave men long ago faced the same evils. . . . The Psalms, turned into strange languages, their original meaning often lost, live on as a real influence in human life. . . . I know the figures in the tradition may be unreal, their words may be misinterpreted, but the communion is quite a real fact and the student, as he realizes this, feels himself one of a long line of torchbearers. He attains that which is the most compelling desire of every human being, a work in life which is worth living for and which is not cut short by the accident of his own death."

Let me add a thought implicit in Sir Gilbert's words. By his lifelong devotion to his work the student draws to himself unselfish friendships, friendships the intensity and selflessness of which no other human relation affords.

* * *

In the rather mixed tale you have listened to this evening, gentlemen, certain persons have been named to you who may have shared such joys. Franklin, surely; Hales, probably; Hartley, possibly; these had the scholar's creed. Excepting Franklin, we know little of their lives but they lived in the happy dawn of science, undistracted by the onrushing plane or by the iteration of radio or press. They possessed, more fully than we can hope to, a moment of peace after labor, that peace which the busy world filches from us.

Enviously I stand here tonight and, looking into your lives, see there this panacea, the scholar's creed, calculated to serve you a longer term of years than did the Joanna Stephens' medicines in their day. To each of you, kind sirs, it is my earnest wish that you live long and that this, your faith, abide with you.

* * *

Your Christian faith I have not the hand to touch nor the wit to argue. We are all aware that our doubting generation carries its investigations into Natural Theology only so far as to echo the most misleading words that Francis Thompson ever wrote:

"I dimly guess what Time in mists confounds;
Yet ever and anon the trumpet sounds
From the hid battlements of Eternity.
Those shaken mists unsettle, then
Round the half-glimpsed turrets wash again."

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DEATHS OF FELLOWS

HUEY, ARTHUR JOHN: 580 Park Avenue, New York City; born in Newark, New Jersey, April 12, 1880; died in New York City, September 29, 1942; graduated in medicine from New York University and Bellevue Hospital Medical College in 1902; elected a Fellow of the Academy March 6, 1919.

Dr. Huey was consulting otolaryngologist to the U. S. Public Health Service Marine Hospitals at Ellis Island and at Stapleton, Staten Island. He was a Fellow of the American Medical Association and a member of the State and County Medical Societies.

MALONEY, EDWARD ROBERT: 515 Park Avenue, New York City; born in Norwich, Connecticut, February 6, 1874; died in New York City, October 5, 1942; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1896; elected a Fellow of the Academy February 5, 1920; served the Academy as Chairman of the Section of Dermatology and Syphil-

ology, 1927-28; as a member of the Committee on Admission from 1939 through 1941; and, as Chairman of that Committee during 1941; he was also a member of the Council; and was a member of the Committee on Medical Information in 1942.

Dr. Maloney was emeritus professor of dermatology and syphilology at New York University College of Medicine, consulting dermatologist to Bellevue Hospital, Elizabeth A. Horton Memorial Hospital at Middletown, New York Foundling Hospital, New York Infirmary for Women and Children, Pilgrim State Hospital at Brentwood, and visiting dermatologist to the St. Vincent's Hospital. He was a Fellow of the American Medical Association, a diplomate of the American Board of Dermatology and Syphilology, and a member of the American Academy of Dermatology and Syphilology, the American Dermatological Association, and the State and County Medical Societies.

In 1907 Dr. Maloney joined the National Guard of New York as Captain in the Medical Corps and in 1916 saw service on the Mexican border. In the first World War he served in Belgium and was promoted to the rank of Lieutenant-Colonel. In 1924 he was commissioned Colonel in the Medical Corps Reserve.

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